Patent
Attorney's Docket No. 020325-053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Reijo J. BACKSTROM *et al.*	)	
	)	
Patent No.: 5,446,194	)	
Issue Date: August 29, 1995	)	**ATTN: Box Patent Extension**
	)	
Application No.: 08/121,617	)	
Filed:	)	
	)	
For: PHARMACOLOGICALLY ACTIVE ACTIVE CATECHOL DERIVATIVES	)	

TRANSMITTAL AND APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

This application is submitted by including an original, a certified copy and three working copies. Each copy contains five Exhibits:

Exhibit 1 - FDA Approval Letter (4 pages)
Exhibit 2 - Copy of Assignment (2 pages)
Exhibit 3 - U.S. Patent No. 5,446,194 (22 pages)
Exhibit 4 - Maintenance Fee Payment (1 page) and
Exhibit 5 - Copy of the Power of Attorney (4 pages)

Pursuant to § 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the provisions of 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, the owner of record of U.S. Patent No. 5,446,194 ("the '194 Patent") requests that the term of the '194 Patent be extended 416 days to expire on October 19, 2013. The '194 Patent issued on August 29, 1995 on patent application Serial No. 08/121,617. The '194 Patent would, in view of GATT, and in the absence of an extended term, expire on August 29, 2012. The patent is assigned of record to Orion-yhtymä Oy, Orionintie 1, 02200 Espoo FINLAND (hereinafter referred to as "Applicant"). "Orion Corporation" or "Orion" is the parallel English business name to Orion-yhtymä Oy, and is also used in this application.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740 in §§ I-XVII.

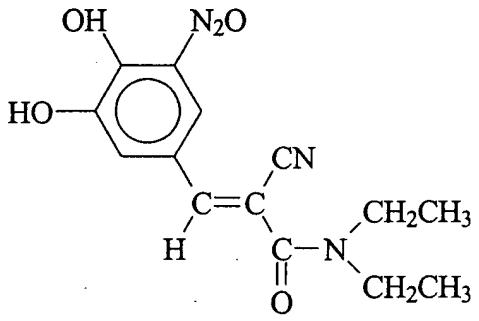
I. APPROVED PRODUCT

The approved product is COMTAN®. The active ingredient is entacapone.

Entacapone is designated chemically as (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide or (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

The empirical formula of entacapone is $C_{14}H_{15}N_3O_5$ and has a molecular weight of 305.29 daltons.

The structure of entacapone is as follows:



Mechanistically, COMTAN® is an inhibitor of catechol-O-methyl transferase (COMT), an enzyme involved in the metabolism of catecholamine neurotransmitters and related drugs.

COMTAN® is a pharmaceutical for treating patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing off" (so-called "fluctuating" patients). The approved product is marketed in the form of a 200 mg tablet to be used as an adjunct therapy to levodopa/carbidopa to treat patients with idiopathic Parkinson's Disease.

II. APPLICABLE FEDERAL STATUTE

The approved product, COMTAN®, was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA") 21 U.S.C. § 301 *et seq.*

Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

III. PRODUCT APPROVAL DATE

The approved product, COMTAN®, received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to § 505(b) of the FFDCA on October 19, 1999. See Exhibit 1 (APPROVAL LETTER FOR COMTAN®).

IV. IDENTIFICATION OF DRUG PRODUCT INGREDIENTS

In accordance with 37 C.F.R. § 1.740(a)(4), the active ingredient of COMTAN® is entacapone. Entacapone has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

V. APPLICATION FILING DEADLINE

The present application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day on which the application can be submitted is December 20, 1999 (December 18, 1999 is a Saturday).

VI. PATENT FOR WHICH EXTENSION IS SOUGHT

The patent for which an extension is being sought is U.S. Patent No. 5,446,194 ("'194 Patent"), which issued on August 29, 1995, in the names Reijo J. BACKSTROM, Kalevi E. HEINOLA, Erkki J. HONKANEN, Seppo K. KAAKKOLA, Pekka J. KAIRISALO, Inge-Britt Y. LINDEN, Pekka I. MANNISTO, Erkki A. O. NISSINEN, Pentti POHTO, Aino K. PIPPURI and Jarmo J. PYSTYNEN. The patent is assigned of record to Orion-yhtymä Oy, Orionintie 1, 02200 Espoo, FINLAND (for copy of Assignment, see Exhibit 2). The reel and frame number for the assigned patent is 4820/0619.

The application for the '194 Patent was filed September 16, 1993 and claims the benefit of priority under 35 U.S.C. § 120 dating back to November 27, 1987. Since this

patent was filed before June 8, 1995, the effective date of the Uruguay Round Agreements Act, it is entitled to a patent term of the longer of twenty (20) years from the earliest effective application U.S. filing date or seventeen (17) years from the patent issue date. For the '194 Patent, a patent term of seventeen (17) years from the issue date of August 29, 1995 is longer. The patent would thus expire, absent term extension, on August 29, 2012.

VII. COPY OF PATENT

A copy of the '194 Patent is enclosed herewith as Exhibit 3, including the entire specification and the claims.

VIII. COPY OF CERTIFICATE OF CORRECTION, DISCLAIMERS, MAINTENANCE FEE PAYMENT RECEIPTS OR REEXAMINATION CERTIFICATES

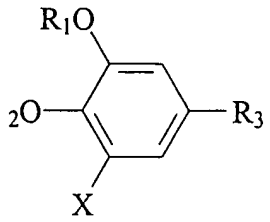
There are no certificate of correction, disclaimer or reexamination certificate for the '194 Patent. A copy of one maintenance fee payment receipt is enclosed in Exhibit 4.

IX. SHOWING THAT PATENT CLAIMS APPROVED PRODUCT

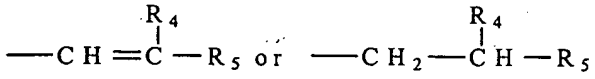
U.S. Patent No. 5,446,194 claims the approved COMTAN® product.

All four of the claims of the '194 Patent encompass the approved product as discussed in detail below:

1. A compound according to formula I



wherein R_1 and R_2 independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents nitro or cyano and R_3 represents



wherein R_4 represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R_5 represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof.

Entacapone has an R_4 group which is cyano and an R_5 group which is a carbamoyl substituted with an alkyl of 2 carbon atoms. Thus, Entacapone is encompassed by Claim 1.

2. The compound according to claim 1, wherein R_4 is cyano and R_5 is carbamoyl which is unsubstituted or substituted with alkyl of 1 to 3 carbon atoms.

Entacapone has an R_4 group which is cyano and a R_5 group which is a carbamoyl substituted with an alkyl of 2 carbon atoms. Thus, Entacapone is within the scope of Claim 2.

3. N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

Entacapone can be chemically designated as (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, which is a stereoisomer of the compound recited in Claim 3. Thus, the approved product is encompassed by Claim 3.

> 4. A compound selected from the group consisting of 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide and N-isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide.

Entacapone can be chemically designated as (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, which is a stereoisomer of a compound recited in Claim 4, *i.e.,* N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide. Thus, the approved product is within the scope of Claim 4.

X. INFORMATION PURSUANT TO 35 U.S.C. § 156(g)

The information required by 37 C.F.R. § 1.740(a)(10)(i) is set forth below.

An Investigational New Drug ("IND") application was filed by Orion-yhtymä Oy for entacapone on September 5, 1991. The IND became effective on November 29, 1991, eighty-five (85) days after the date of receipt of the IND. The IND number assigned to entacapone was IND 37,771.

A New Drug Application ("NDA") was filed by Orion-yhtymä Oy on January 2, 1998. The NDA number assigned to the application for COMTAN® was NDA 20-796. The NDA was approved on October 19, 1999.

Further, the above-identified patent is eligible for an extension of patent term since the following requirements of 35 U.S.C. § 156(g) are met:

(1) the above-identified patent has not expired prior to the filing of this application for extension of patent term;

(2) the term of the patent has never been extended;

(3) the application for extension of patent term is being submitted by the agent for the owner of record of the '194 Patent for which a patent term extension is sought, who is a patent attorney authorized to practice before the U.S. Patent and Trademark Office (see attached Power of Attorney (Exhibit 5)), and who has general authority from said owner to act on behalf of said owner in patent matters including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. § 1.740;

(4) the product has been subject to a regulatory review period before its commercial marketing or use;

(5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

XI. ACTIVITIES DURING REGULATORY REVIEW PERIOD

Significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the dates applicable to such activities are as follows.

TABLE 1

Investigational New Drug (IND) Application (37,771) Entacapone Related Events

Date	Submission contains:
September 5, 1991	Investigational new drug application
October 17, 1991	Response to FDA request: -Changes to the report of Hazleton
October 28, 1991	Response to FDA request for more information: - Final Study report 6753-544/23, Hazleton
December 2, 1991	Oxford was notified by FDA that the clinical study could be initiated
December 10, 1991	-Reference to the December 2, 1991 telephone conversation with the FDA a protocol amendment was provided - amendment 3 Dec. 91 / HH910010/0
April 20, 1992	- Protocol amendment HH920001/0 - Final protocol HH920006/1 - FDA FORM 1572/LeWitt - Rationale for 293928
September 10, 1992	Initial written report, safety report: - AER, patient 02
September 22, 1992	- Protocol amendment HH920009/1
January 4, 1993	Annual Progress Report - AKRO920034/1
January 5, 1993	Initially written report, safety report, S-008 - SAE, patient 15, USA
January 11, 1993	Request for FDA meeting to review the results of the clinical studies summarized in - Status report KJ9200006/0

Date	Submission contains:
February 8, 1993	Follow-up to a written report S-008: - completed form FDA 1639
February 17, 1993	Correspondence from the FDA, Ms. Katurah Higgins concerning Chemistry deficiencies in the IND
February 19, 1993	List of people on behalf of Orion attending the March 3, 1993 meeting
March 2, 1993	Initial written report, safety report: - AER, patient 3
March 3, 1993	FDA meeting
March 26, 1993	Initial written report, safety report - AER, patient 7 - Amended protocol SR93003
March 29, 1993	- Minutes of the FDA meeting 3.3.93 - Final protocol AKRO920026/1 - Final protocol HH920011/1
May 14, 1993	- Overheads used on Meeting March 3, 93 - Curriculum/ Nutt, LeWitt, Kohler - 7A, 3.5.93 ILLA930001/1 - 7B, 3.5.93 - 7C, 3.5.93 - Final protocol TANA930016
August 24, 1993	- Curriculum/ Thulin, FORM 1572 - Curriculum/ Green, FORM 1572 - Amendment 1, HH93004/1
August 25, 1993	Initial written report: Study 2939035 - SAE, subject 004, Finland - SAE, subject 008, Finland - Final protocol AKRO930003/1 Study 2939039 -SAE, subject 10, Finland - Study protocol TANA930016/1

Date	Submission contains:
October 14, 1993	- protocol AKRO930001/1, - curriculum/Eidelberg, - Inv. Br. June 1993
December 13, 1993	Information amendment (Chemistry) Response to the chemistry deficiencies outlined in Ms. Higgins'correspondence of 17 February 1993 - amendment to IND ILLA930017/0
January 5, 1994	Information amendment, results of two toxicology studies - 59/930295, Huntingdon - 58/930792, Huntingdon
January 6, 1994	Annual Progress Report - AKRO930058/1
January 27, 1994	Request for End-of-Phase 2 meeting
February 22, 1994	-Final protocol, HH930008/1, Study 2939044 - CV's (17 investigators)
February 25, 1994	Information amendments: -Amendment to IND, Item 7, ILLA9940010
March 18, 1994	Information amendments (clinical) follow-up to a written report: - Updated investigator's brochure - Study report 2939042 (TANA930025/1) - CV / Nutt, LeWitt, Koller
March 25, 1994	Initial written report - SAE, patient 008, Finland - protocol synopsis to study 293930
March 31, 1994	Response to FDA request for info .- Discoloration of the urine by E. - Minutes of the FDA meeting 3.3.93
April 4, 1994	Initial written report - SAE, patient 012,
April 12, 1994	Change in protocol - Amendment I to 2939044 (HH940003/1)

Date	Submission contains:
May 3, 1994	Request for end of phase 2 meeting with the division of neuropharmacological drugs. - Summary of data on the development of Entacapone, KJ940001/0
June 22, 1994	Other: Adverse experiences - SAE: patient 21, 293930, ENT9411, Finland - SAE, patient 286, Seesaw-study, USA
June 23, 1994	Conference call minutes, June 2, 94: - discoloration of the urine by Entacapone - blindness evaluation form - research subject consent form
July 12, 1994	- Form 1572 and CV of Dr. Lang - Second amendment to study protocol No 2939044, HH94005/1 - third amendment to study protocol No 2939044, HH94006/1
July 13, 1994	Transfer of clinical study monitoring - Orion-Farmos, Kansas established
July 14, 1994	Follow-up to a written report: - SAE, patient 286, USA - form 1572 for Dr. A. Feigin
August 5, 1994	Information on foreign clinical study: - protocol 2939033, MIVA930001/1 - list of centers and investigators, April 25, 94 - status May 9, 94 - FDA 1572's and CV's
August 12, 1994	A Letter from Dr. Leber, comments on the Biopharmaceutics section
September 12, 1994	Initial written report -SAE, patient 4109, Sweden, 2939034, ENT9420
September 29, 1994	Response to FDA request for information. Referring to FDA review of the biopharmaceutics section of supplement submission on Entacapone (S-030)
September 28, 1994	Initial written report, follow-up to a written report - SAE, patient 4103, Sweden, 2939034, ENT9420 - AER, 2939044, SEESAW, patient 184, USA
October 13, 1994	Follow-up to a written report: - SAE, patient 184, SEESAW, USA, ENT9422

Date	Submission contains:
October 14, 1994	Change in protocol: - study protocol 2939054
November 28, 1994	Additional information: - 1572 Forms
November 29, 1994	Information amendments: - Toxicological summary explaining the study results (HERA940005) - Investigator's letter / findings of the rat carcinogenicity study - study protocol IRI 450970: 104 week carcinogenicity study in rats by gavage
December 7, 1994	Initial written report: - AER, 2939044, patient 370, ENT9437, Canada - SAE, 2939044, patient 364, Canada - AER, 2939034, patient 4605, ENT9434, Sweden Follow-up to a written report: - AER, 2939034, patient 4202, ENT9423, Sweden - SAE, 293930, patient 004, ENT941, Finland - SAE, 2939044, patient 366, ENT9432, Canada - AER, 293930, patient 008, ENT943, Finland (sent to FDA as S-026) - AER, 293930, patient 012, ENT944, Finland (sent to FDA as S-028) - AER, 293930, patient 021, ENT9411, Finland (sent to FDA as S-031)
December 13, 1994	Response to FDA request for information: - C.V.'S for subinvestigators Lauren Abrey, Carolyn Cook, Karin Graefe
December 28, 1994	General correspondence: - phase III protocol: request for FDA's opinion of the number of patients and duration of treatment
January 5, 1995	Initial written report: - SAE, subject 262, 2939054, USA
January 13, 1995	New protocol: - 2939061, HH940010/1 21.12.94
January 13, 1995	Initial written report: - SAE, 2939044, patient 270, USA - AER, 2939033, patient 4105, Sweden (ENT9414) - AER, 293930, patient 20, Finland (ENT9412)
January 13, 1995	Annual report: - NINI940001/0

Date	Submission contains:
January 17, 1995	Clinical plan: - Outline of continuation of clinical plans
January 23, 1995	Revised 1572s of investigators: - Juncos, Greene, Kurlan, Jankovic, Shannon
February 3, 1995	Letter from FDA, statistical comments on protocol 2939044
February 21, 1995	Other information: request for meeting, biopharmaceutics information - Pre-meeting information MKAH940007 - outlines of protocols 2939057, 29390582939054 - tablet and raw material batches used in clin. studies
February 27, 1995	Change in protocol: - 2939061, amend I, HH950002/1
February 27, 1995	Change in protocol: - 2939054, amend I, HH950001/1
February 28, 1995	Initial written report, safety report: - AER, patient 106, 2939054, USA
March 7, 1995	Initial written report, safety report: - AER, subject 4201, 2939034, Sweden
March 7, 1995	Follow-up to a written report: - letter: A Gordin, 27.2.95 to clarify the circulatory collapse adverse events of patients listed in the annual report (S-021) - patient 2/293913 - patient 18/293926 - patient 4/2939033 - patient 8/293915A
March 16, 1995	Other: 1572 forms and Curricula Vitaes for 17 investigators
March 20, 1995	Initial written report, follow-up to a written report: - AER, patient 4303, 2939034, Sweden
March 23, 1995	Initial written report, follow-up to a written report: Safety report - AER, patient 3403, 2939034, ENT9510, Norway
March 30, 1995	Follow-up to a written report: - AER, patient 364, Seesaw, Canada
March 31, 1995	Other: Agenda/list of attendees for teleconference to be held April 18, 95

Date	Submission contains:
April 4, 1995	Initial written report, safety report: - AER, patient 041, 2939054, ENT9517, USA
April 7, 1995	Other: Investigator's Brochure March -95, MKAH950008/1
April 11, 1995	Other: Study report 2939060, TANA950003/1
April 17, 1995	Follow up to a written report, safety report: - AER patient 3404 (2939034, ENT9510, Norway) - SAE patient 330 (2939044, USA) - AER patient 061 (2939054, ENT9520, USA)
April 18, 1995	Telephone conversation R. McCormack - R. Baweja, re-scheduling of the teleconference
April 19, 1995	Other: Confirmation for the Biopharmaceutics Teleconference
April 21, 1995	Biopharmaceutics Teleconference
April 25, 1995	Initial written report, safety report: - AER, patient 107 (ENT9522, USA)
April 25, 1995	Other: Confirmation of FDA Meeting to discuss Biopharmaceutics Issues, May 12, 1995
May 3, 1995	Other: Request for a meeting with the Neuropharmacology Division at FDA - FDA O-F correspondence 1994, HH950003/0
May 3, 1995	Other: revised 1572 forms (J. Juncos, C. Shults)
May 5, 1995	IND safety report, initial written report: - AER, patient 029 (ENT9524, USA)
May 12, 1995	FDA Meeting to discuss Biopharmaceutics Issues
May 25, 1995	Initial written report, safety report: - AER, patient 2118 (2939033, Finland) - AER, patient 330 (ENT9530, 2939054, USA)
June 2, 1995	Initial written report, safety report: - AER, patient 012, 2939054, ENT9528, USA

Date	Submission contains:
June 5, 1995	Other: meeting package information - Meeting with the Neuropharmacology Division at FDA: - List of O-F and Oxford Res Attendees - Background for items to discuss, MKAH9500009/1 - Detailed supportive information, MKAH950010/1
June 8, 1995	Other, revised FDA form 1572s: - CV / James Bennett Information amendments, pharmacology / toxicology: - LSR report 94/ORP040/0561 - LSR report 94/ORP041/0686 - LSR report 94/ORP02/0583 - LSR report 94/ORP03/0813
June 15, 1995	Initial written report: - AER, patient 302, 2939061 (ENT532, USA)
June 19, 1995	F. Abramek requests for copies of submission S-076
June 19, 1995	Response to FDA request for information: copies of submission S-076
June 20, 1995	IND safety reports, initial written report: - AER, patient 012 (ENT9528, USA) - AER, patient 307 (ENT9535, USA)
June 27, 1995	Other: response to statistical issues, HERI950001
July 10, 1995	Other: draft FDA meeting minutes, May 12, 1995 HH950005/1
July 18, 1995	Information amendments: pharmacology/toxicology: - HRC report 68/943243
July 18, 1995	Response to FDA request (meeting on May 12, 1995) for information, study reports: - 2939035, SIRA940001/1 - 293925, AKRO940007/1 - 2939047, AKRO940015/1 - 293905, AKRO910016/0 - 293920, AKRO930011/1 - 2939050, TANA940006/1 - Dissolution data, 9.6.95

Date	Submission contains:
July 21, 1995	Information amendments: pharmacology/toxicology (requested on meeting May 12, 1995): - CR92032030058, MAKA920005 - Wikberg et al, -94 - Wikberg et al, -93 - Wikberg et al, -93 - CR90032870017, TW900003 - CR89032870004, AKRO890005 - CR89032870005, TW900001 - CR91032870033, TW910003 - Metabolism, MKAH950012 - CR95031210228, TW950001 - Protein binding, MKAH950011§
July 25, 1995	IND safety reports, initial written report: - AER, patient 189, 2939054 (ENT9543, USA)
August 2, 1995	Initial written report, safety report: - SAE, patient 4202 (2939034, ENT9546, Sweden)
August 11, 1995	FDA Meeting
August 17, 1995	Initial written report, safety reports: - SAE, patient 0158 (2939052, ENT9544, Finland) - SAE, patient 409 (2939061, ENT9549, USA)
August 23, 1995	Initial written report, safety reports: - SAE, patient 0552 (2939052, ENT9555, Finland) - SAE, patient 404 (2939061, ENT9550, USA)
September 6, 1995	Initial written report, safety reports: - SAE, patient 326 (2939054, ENT9556, USA) - SAE, patient 302 (2939061, ENT9532, USA)
September 12, 1995	Follow up to a written report, safety report: - SAE, patient 411 (2939061, ENT9566, USA) - SAE, patient 370 (2949044, Canada)
September 15, 1995	Other: Meeting Minutes Aug. 11, 1995 + overheads used during the meeting
September 19, 1995	Initial written report, safety report - SAE, patient 281 (2939054, ENT9574), USA - SAE, patient 42 (2939054, ENT9575), USA

Date	Submission contains:
October 3, 1995	Other: FDA request on Meeting Aug 11, 1995. Statistical analysis plans. - TUKY950001 (2939033) - HERI950002 (2939044)
October 10, 1995	Initial written report, safety report: - AER, patient 3316 (2939034, ENT9580, Norway) - AER, patient 0158 (2939052, ENT9581, Finland)
October 12, 1995	Safety report: - AER, patient 370 (2939044, Canada)
October 18, 1995	Initial written report, follow up to a written report, safety report: - AER, patient 0501 (2939052, Finland) - AER, patient 0109 (2939052, Finland) - AER, patient 262 (2939054, USA)
October 31, 1995	Initial written report, safety report: - AER, patient 326 (2939054, USA)
November 8, 1995	Initial written report, safety report: - AER, patient 0158 (2939052, Finland)
November 27, 1995	Follow-up to a written report, safety report: - AER, 2939034, patient 3316, Norway (ENT9580) - AER, 2939052, patient 0158, Finland (ENT9581) - AER, 2939054, patient 307, USA (ENT9535)
November 28, 1995	Revised 1572s for - 2939054: J. Jankovic, G. Paulson, R. Pahwa, M. Mark - 2939061: R. Pahwa CV - 2939054, 2939061: J. Hubble
December 28, 1995	Initial written report: - AER, 2939054, patient 281, USA (ENT9574) Initial and follow-up to a written report: - AER, 2939034, patient 4702, Sweden (ENT9596)
January 19, 1996	Initial written report: - SAE, 2939054, patient 041, USA (ENT963) - SAE, 2939052, patient 0301, FIN (ENT964) Correction page regarding S-102 (Dec 28, 95), AER, 2939054, patient 281, USA (ENT9574) - page III treatments

Date	Submission contains:
February 1, 1996	Follow-up to a written report: - SAE, patient 42, 2939054, USA (ENT9575)
February 2, 1996	Annual report MKAH950014/1
March 5, 1996	Initial written report: - SAE, patient 0301, 2939052, Fin (ENT964) Follow-up to a written report (S-103) - SAE, patient 1610, 2939052, Fin (ENT9621) other: revised 1572: - Dr. Margery Mark, 2939044
March 19, 1996	Follow-up to a written report (S-102): - SAE, patient 4702, 2939034, SWE, ENT9596
March 29, 1996	Follow-up to a written report (S-070): - SAE, patient 107, 2939054 USA, ENT9522
April 3, 1996	Initial written report: - SAE, patient 4105, SWE, 2939033, ENT9414 Follow-up to a written report (S-108): - Corrected page, patient 107, 2939054, ENT9522 (Sponsor's summary)
April 26, 1996	Initial written report: - SAE, patient 283, 2939054 USA, ENT9647
April 30, 1996	Other: - revised Investigator's Brochure MKAH960001/1, January 1996
May 1, 1996	Initial written report: - SAE, patient 411, 2939061 USA, ENT9649
May 6, 1996	Follow-up (S-075, S-080): - SAE, Patient 012, 2939054, USA, ENT9528 Follow-up (S-103, S-106): - SAE, patient 0301, 2939052, FIN, ENT964

Date	Submission contains:
July 2, 1996	Information amendments: Pharmacology/Toxicology - Internal study report F93061210438, LESO950003, Finland 1996, vol 1 - IRI report 11353, Scotland 1996, vol 2-3 - IRI report 11312, Scotland 1996, vol 4-5 - F95101210622, KRHA960007, Finland 1996, vol 6 - J.P. Finn: Histological study report, Finn International, England 1995, vol. 6 - Huntingdon Life Sciences report 95/ORP048/0300, England 1995, vol. 6 - Internal study report F95101210605, Finland 1996, vol. 6 - Huntingdon Life Sciences report 95/ORP050/0500, England 1995
July 12, 1996	Initial written report: - Expedited AER, patient 0755, Finland, 2939052, ENT9688 initial
July 19, 1996	Initial written report: - Expedited AER, patient 4204, Sweden, 2939034, ENT96102 initial
August 8, 1996	Initial written report: - Expedited AER, patient 0402, 2939063, Germany, ENT96111 initial Follow-up to a written report (S-116): - patient 0755, Finland, ENT9688, 2939052, sponsor summary Other: revised 1572 for Dr. Kurth, 2939054
August 29, 1996	Other: revised 1572 for Dr J. Jankovic + CV for Dr. C. Sankhla (sub-investigator)
September 6, 1996	Initial written report: - Expedited AER, patient 1501, 2939063 Germany, ENT96131
September 25, 1996	Follow-up to a written report (S-120) - Expedited AER, patient 1501, 2939063 Germany, ENT96131
October 2, 1996	Follow-up to a written report (S-116) - 2939052: Expedited AER, patient 0755, Finland, ENT9688 initial - 2939054: Revised 1572 for Dr. Kurlan
October 31, 1996	Information amendment: - Chemistry, manufacturing and controls, ILLA960009/1
December 16, 1996	Initial written report: - Expedited AER, patient 0413, USA, ENT96182 (death)

Date	Submission contains:
December 17, 1996	Initial written report: - Expedited AER, patient 1651, Germany, ENT96179
January 3, 1997	Follow-up to a written report - 2939054: Expedited AER, patient 029, ENT9524, USA, (S-073) - 2939054: Expedited AER patient 283, USA, ENT9647 (S-110) - 2939052: Expedited AER, patient 0109 2939052, Finland, (S-097)
January 3, 1997	Information amendments: chemistry and microbiology: - Huuhtanen, Dec. 17, 1996 (changing the status of Enta-III-X from an intermediate compound to a starting material)
January 3, 1997	Initial written report: - 2939062: Expedited AER, patient 1911, Finland, ENT971 - 2939065: Expedited AER, patient 0657, UK, ENT96185 - 2939073: Expedited AER, patient 1558, Germany, ENT96186
January 13, 1997	Revised 1572's: - 2939054: Dr. J. Tertrud, Dr. A. Lang, Dr. J. Hammerstad - 2939061: Dr. J. Hammerstad
January 22, 1997	Initial written report: - 2939062: Expedited AER, patient 0456, Finland, ENT9711 (death)
January 23, 1997	Information amendments: chemistry and pharmacology: Item 7a, M. Tuominen Dec. 30, 1996
January 31, 1997	Initial written report: - 2939034: Expedited AER, patient 4402, Sweden, ENT9722 (death)
February 10, 1997	Initial written report - 2939073: Expedited AER, patient 1571, ENT9729, Germany
March 6, 1997	Annual report 1996, HEJI970001/1
March 6, 1997	Follow-up to a written report - 2939034: Expedited AER, patient 4402, ENT9722, Sweden (S-133) - 2939061: Expedited AER, patient 411, ENT9566, USA (S-091)
March 21, 1997	New correspondence: a summary of the telephone conversations between Dr. Rzeszotarski/FDA and P. Kosmoski/Oxford (January 13, 15 and 23, 1997)

Date	Submission contains:
April 3, 1997	Follow-up to a written report - 2939073: Expedited AER, patient 1571, Germany, ENT9729 (S-134) Revised 1572's - 2939054: Dr. M. Kurth, Dr. J. Juncos
May 13, 1997	Initial written report: - 2939065: Expedited AER, patient 1103, GBR, ENT9771 - 2939054: Expedited AER, patient 261, USA, ENT9773
May 29, 1997	Other: Documentation of the telephone conversation on May 27, 1997, between Dr. Robert McCormack and Ms. Teresa A. Wheelous where the results of FDA's review of S-143 were transmitted
May 30, 1997	Initial written report: - 2939054: Expedited AER, patient 314, USA, ENT9793 Follow-up to a written report: - 2939062: Expedited AER, patient 1911, FIN, ENT971
June 17, 1997	Initial written report: - Expedited AER, patient 167, USA, ENT970107
July 25, 1997	Follow-up to written report: - 2939061: Expedited AER, patient 409, ENT9549 (initial S-088) - 2939073: Expedited AER, patient 1558, ENT96186 (initial S-127)
December 10, 1997	Initial written report: - 2939073: expedited AER, patient 2551, DEU, ENT97192, CTX 06043/0019/A
March 12, 1998	Annual report 1997, PAWA980001/1
March 19, 1998	Initial written report: - Expedited AER, patient 1151, USA, ENT9839, CTX 06043/0019/A
May 4, 1998	Change in protocol: - Second amendment to study protocol 2939054, 21.10.97 - Second amendment to study protocol 2939061, 21.10.97 Revised 1572s, 2929054: S. Factor, P. Greene, J. Growdon, M. Kurth, J. Juncos, A. Lang, M. Mark, G. Paulson, R. Pahwa, K. Shannon, R. Kurlan, J. Jankovic, C. Waters, J. Hammerstad, R. Kurlan Revised 1572s, 2929061: R. Pahwa, J. Hammerstad

Date	Submission contains:
June 11, 1998	Information amendments: chemistry /microbiology: CMC (SAMA980002)
July 7, 1998	Initial written report: - 2939034: expedited AER, patient 2112, ENT9882
July 15, 1998	Initial written report: - 2939069: expedited AER, patient 0101, ENT9889 Revised 1572s, 2939054: Roger Kurlan, Margery Mark (corrected copy of S-158 received on September 3, 1998, previous version had Dr. Kurlan's 1572 form omitted)
August 6, 1998	Safety report: Initial written report - 2939069: expedited AER, patient 0559, GBR, ENT9890 - 2939073: expedited AER, patient 0152, AUT, ENT9892
August 26, 1998	Safety report: Initial written report - 2939073: expedited AER, patient 2102, DEU, ENT98103
August 28, 1998	Safety reports: Follow-up to a written report - 2939073: expedited AER, patient 0152, AUT, ENT9892 - 2939069: expedited AER, patient 0101, GBR, ENT9889 (death) - 2939065: expedited AER, patient 1103, GBR, ENT9771 - 2939054: expedited AER, patient 247, USA, ENT9831 (death)
September 3, 1998	- letter regarding S-158, S160, S-161
October 19, 1998	Safety report, Initial written report - 2939054: expedited AER, patient 045, USA, ENT98127 - letter dated October 28, 1998
March 1, 1999	Change in designation of US Agent - letter dated: February 24, 1999
March 1, 1999	Initial safety report - sudden death - expedited AER, patient MZ, DEU, ENT9914 - letter dated: February 26, 1999
April 12, 1999	Initial safety reports - ENT9951, GBR, patient died - ENT9916, SWE - ENT9953, DEU

Date	Submission contains:
April 16, 1999	Initial safety reports - ENT9963, GBR, patient died - ENT9956, GBR
April 23, 1999	Initial safety reports - ENT9965, GBR - ENT9983, GBR
April 26, 1999	Follow-up safety report - ENT9983, GBR
April 27, 1999	Initial safety reports - ENT99100, GBR - ENT99101, GBR
May 15, 1999	Initial safety reports - ENT99123, DNK - ENT99124, DNK
June 11, 1999	Initial and follow-up safety report - ENT992, GBR
June 18, 1999	Annual report -98, 100 and 200 mg tablets. Period: 16 Nov 1997 - 15 Nov 1998, AIHO990001/1, 8.6.99
July 1, 1999	Initial safety report - ENT99168, GBR - ENT99177, IRL
July 8, 1999	Initial and follow-up safety report - ENT99173, GBR
July 13, 1999	Letter of cross-reference
July 23, 1999	Follow-up safety report - ENT99177, IRL
August 6, 1999	Initial safety report - ENT99221, SWE - ENT99214, DEU
August 19, 1999	Initial safety report - ENT99227, GBR

Date	Submission contains:
August 27, 1999	Initial safety report - ENT99230, DEU
September 3, 1999	Initial safety report
September 13, 1999	Initial and follow-up safety report - ENT99231, GBR
September 15, 1999	Initial safety report - ENT99298, DEU
September 17, 1999	Response to requests of 13.9.99 regarding adverse event report - ENT99227 (S-178)
October 13, 1999	Initial safety report

TABLE 2

New Drug Application (20-796)

COMTAN® Tablet, 200 mg (Entacapone) Related Events

Date	Responsible	Subject
December 4, 1996	Orion / Oxford Research Int.	Request for pre-NDA-meeting
February 19, 1997	Orion / Oxford	Pre-NDA-Meeting Package
March 6, 1997	Orion / Oxford	Pre-NDA-Meeting List of Attendees
March 13, 1997	Orion / Oxford	Correction to the Pre-NDA-Meeting Package
March 20, 1997		Pre-NDA-Meeting
April 4, 1997	Orion / Oxford	To confirm the meeting of CMC-issues between Orion and Oxford personnel and the FDA chemists
April 7, 1997	Orion / Oxford	Response to FDA request for information during the Pre-NDA-Meeting
April 14, 1997		Meeting with FDA to discuss the CMC-issues
April 30, 1997	Orion / Oxford	Meeting Minutes, March 20, 1997 and April 14, 1997 were sent to FDA
May 29, 1997	Orion / Oxford	Documentation of the telephone conversation on May 27, 1997, between Dr. R. McCormack and Ms. T. Wheelous where the results of FDA's review of information provided April 7 were transmitted
October 24, 1997	Orion	Appointment of new agent Target Research Associates to act as the US agent for the New Drug Application (#20,796) Comtan® Tablet, 200 mg (Entacapone) Appointment Letter was included in the NDA submission
October 24, 1997	Orion / Target	Initial Filing of New Drug Application (20-796) Comtan® Tablet, 200 mg (Entacapone)
October 28, 1997	FDA / T. Wheelous	Request from FDA for a diskette of package insert.

Date	Responsible	Subject
October 30, 1997	FDA	Date of Application 24 October 1997 Date of Receipt of Application 24 October 1997
October 30, 1997	Orion / Target	Three additional desk copies were sent to the FDA as requested by phone
November 4, 1997	Orion / Target	A diskette of Annotated Package Insert was sent to Theresa Wheelous
December 1, 1997	FDA / J. Knudsen	Medical questions regarding review of Entacapone NDA for fileability
December 3, 1997	FDA / T. Wheelous	T. Wheelous required additional information to determine the fileability of the Entacapone NDA. 1. Submission of patient narratives 2. Electronic submission of the carcinogenicity study data
December 4, 1997	FDA / T. Wheelous	T. Wheelous informed that the Entacapone NDA was not fileable
December 5, 1997	Orion / Target	Electronic submission of the carcinogenicity study data
December 11, 1997	FDA / J. Choudhury	Results of statistical reviewer of Entacapone
December 14, 1997	Orion / Target	Submission of narrative summaries
December 15, 1997	FDA / Rusty Katz	Dr. Rusty Katz contacted to discuss the reasons for refusal
December 19, 1997	Orion / Target	The sponsor requested FDA to issue a refusal to file letter
December 23, 1997	FDA / P. Leber	Letter to refuse the file
December 23, 1997	Orion / Target	Entacapone NDA resubmitted to the FDA
December 30, 1997	Orion / Target	Submission of additional statistical information requested by Dr. Japobrata Choudhury on December 11, 1997
January 2 (8), 1998	FDA	User fee payment was received. Application has been accepted as of January 2, 1998
February 19, 1998	FDA/ T. Wheelous	NDA was accepted for filing

Date	Responsible	Subject
February 23, 1998	FDA / T. Wheelous	Request for additional copies of information
February 27, 1998	Orion / Target	Submission of investigator list for adequate and well-controlled trials contained in NDA 20-796
February 27, 1998	Orion / Target	Additional copies requested on 23 February were sent
April 7, 1998	FDA / T. Wheelous	Request to investigate the Environmental Assessment (EA) for Entacapone NDA
April 20, 1998	FDA / T. Wheelous	Request for additional copies
April 22, 1998	Orion / Target	Additional copies were sent
April 24, 1998	Orion / Target	Environmental Assessment (EA) for Entacapone NDA was replaced with documentation supporting categorical exclusion)
April 30, 1998	FDA / T. Wheelous	FDA could not locate the diskettes for the case report form tabulations
May 1, 1998	Orion / Target	Amendment to add an alternative packaging site for dosage form
May 4, 1998	Orion / Target	Diskettes requested on 30 April 98 were sent
May 6, 1998	FDA / T. Wheelous	Request for Additional Information
May 8, 1998	Orion / Target	Stability Update Amendment on the Dosage Form
May 15, 1998	Orion / Target	Submission of the 120 Day Safety Update Report
June 17, 1998	FDA / T. Wheelous	Request for an additional desk copy of Volume 3 of the 120 day safety update
June 18, 1998	Orion / Target	Copy requested on 17 June was sent
July 29, 1998	FDA / M. Sevka	Request for additional copies of Orion Studies 2939033, 2939044 and 2939052
July 30, 1998	FDA / T. Wheelous	Request for additional copies of study report/SAS data sets Nomenclature committee decision

Date	Responsible	Subject
July 31, 1998	FDA / M. Sevka	Clarification on the coding used for the CRF tabulations
August 3, 1998	Orion / Target	Copies requested on 29 July were sent
August 3, 1998	FDA / M. Sevka	Clarification on the glossary of adverse events
August 5, 1998	Orion / Target	Information requested on 30 and 31 July was sent to FDA
August 7, 1998	FDA / T. Wheelous	Request for SAS Data Sets
August 10, 1998	FDA	FDA's preliminary review (dated August 4) of the CMC section
August 11, 1998	Orion / Target	Information requested on 3 August was sent
August 12, 1998	FDA / J. Choudhury	Request for additional information for the Entacapone
August 14, 1998	Orion / Target	SAS data sets requested on 7 August were sent
August 18, 1998	FDA / J. Choudhury	Follow-up to statistical information
August 18, 1998	FDA / M. Sevka	Questions concerning review of the safety data for the Entacapone NDA
August 19, 1998	FDA / R. Tresley	Request for a list of countries where Entacapone is approved for marketing
August 21, 1998	FDA / R. Tresley	Request for additional information
August 27, 1998	Orion / Target	Partial response to information requested on 12 August was sent
August 28, 1998	FDA + Orion + Fermion	Teleconference concerning the CMC questions
September 10, 1998	FDA / S. Al-Habet	Request for additional information, Study 2939057
September 10, 1998	Orion / Target	Additional information, Study 2939057, was provided
September 10, 1998	Orion / Target	Response to outstanding questions from 12 August
September 10, 1998	Orion / Target	Information requested 18 August was sent to FDA

Date	Responsible	Subject
September 15, 1998	FDA / R. Tresley	Clarification on daily-on-time calculations
September 15, 1998	FDA / S. Al-Habet	Location of individual information
September 16,1998	Orion / Target	Phone call to the FDA concerning the individual information requested on 15 September
September 18, 1998	FDA / T. Wheelous	Request to locate information in the pharmacology/toxicology section
September 21, 1998	Orion / Target	Information requested on 15 September was provided
September 22, 1998	Orion / Target	Information requested on 18 September was provided
September 25, 1998	FDA / J. Choudhury	Clarification for the responses submitted on 27 August and on 10 September J. Choudhury requested a telephone conference
September 25, 1998	Orion-Fermion	Fermion submitted the response for additional information requested on August 25 , 1998
September 28, 1998	FDA + Orion	Teleconference corresponding to request on 25 September
September 29, 1998	FDA / M. Sevka	Clarification of coding of laboratory values for study #33
September 29, 1998	FDA / M. Sevka	Request of glossary of adverse events
September 30, 1998	Orion / Target	Response to coding of laboratory values was provided
September 30, 1998	Orion / Target	Response to August 4, 1998, chemistry comments letter
October 1, 1998	Orion / Target	Individual information requested on 15 September was provided to the FDA
October 7, 1998	Orion / Target	A glossary of adverse events was submitted as requested on 29 September
October 13, 1998	FDA / M. Sevka	Questions regarding the 120-day safety update
October 13, 1998	FDA / S. Al-Habet	Request for individual creatinine clearance values

Date	Responsible	Subject
October 13, 1998	FDA / J. Choudhuryn	Request concerning the unblinding dates
October 15, 1998 (October 27, 1998)	Orion / Target	Response provided to the unblinding dates
October 20, 1998	Orion / Target	Response provided to question on 13 October, 120-day safety update
October 20, 1998	FDA / J. Choudhury	Clarification of statistical comments
October 22, 1998	FDA / J. Chouldhury	Clarification of statistical comments
October 23, 1998	FDA + Orion	Teleconference
October 23, 1998	FDA / M. Sevka	Index of case report forms for all Studies was requested
October 28, 1998	Orion / Target	Minutes of the teleconference held on October 23, 1998 was sent to the FDA
November 3, 1998	Orion / Target	Submission of individual creatinine clearance values as requested on October 13, 1998
November 3, 1998	FDA / J. Chouldhury	Clarification of Statistical Information provided in the NDA
November 3, 1998	FDA / Orion	Teleconference concerning the statistical information requested
November 4, 1998	Orion / Target	Index for case report forms as requested on 23 October was provided
November 5, 1998	FDA/R. Kelley	Clarification: statistical analysis of electronic data and hard copy data in Rat Carcinogenicity Study
November 11, 1998	Orion / Target	Amendment to pending NDA: specifications and test methods for the bulk and packaged drug product
November 12, 1998	Orion / Target	Submission of information requested on November 5, 1998
November 18, 1998	FDA + Orion	Teleconference concerning safety update
November 19, 1998	FDA / M. Heimann	"CMC" changes to the Package Insert and container labels.

Date	Responsible	Subject
November 24, 1998	Orion / Target	Revised Package Insert and Container Labels provided
November 24, 1998	Orion / Target	Submission of Entacapone labeling to be used in the United Kingdom
December 1, 1998	Orion / Target	Letter of authorization allowing Novartis personnel to contact the agency
December 1, 1998		Summary of FDA teleconference on November 18, 1998 and submission of information requested during the teleconference
December 2, 1998	Orion / Target	Updated Methods Validation Package The Methods Validation Package is updated to reflect the CMC changes introduced in Orion's CMC submission of September 30, 1998
December 7, 1998	Orion / Target	Submission of second Safety Update Report
December 21, 1998	FDA / R. Tresley	Data clarification requests
December 22, 1998	Orion / Target	Clarification was provided to Dr. Tresley's request dated December 21, 1998.
December 22, 1998	FDA / R. Tresley	Additional information requested by Dr. Tresley
December 31, 1998	FDA	Approvable Letter
January 6, 1999	Orion / Target	Response to Approvable Letter dated December 31, 1998
January 18, 1999	Orion / Target	Request for a meeting to discuss the NDA approvable letter
January 25, 1999	Orion / Target	Submission of the proposed logo
January 27, 1999	Orion / Target	Submission of meeting package for discussions related to the NDA approvable letter
February 11, 1999	FDA + Orion	Discussion with FDA related to the approvable
February 12, 1999	FDA / R. Tresley	Request of preclinical toxicological data
February 19, 1999	Orion / Target	Requested preclinical tox data was sent to FDA

Date	Responsible	Subject
February 24, 1999	FDA / T. Wheelous	Results of FDA-meeting regarding approvable letter for Entacapone
April 2, 1999		Review clock started, FDA received the complete response
April 16, 1999 (April 19, 1999)	Orion / Target	Submission of complete response to NDA approvable letter
April 22, 1999	Orion / Target	Additional desk copies requested by FDA were submitted
April 28, 1999	FDA / T. Wheelous	Request for additional desk copy of the complete response
April 29, 1999	FDA / T. Wheelous	Response regarding the reporting of adverse events
May 24, 1999	FDA + Orion	Teleconference regarding complete response to NDA approvable letter
May 25, 1999	Orion / Target	Notification of changes made to the Type II DMF # 12,444 for Entacapone
May 26, 1999	FDA + Orion	Follow up to teleconference regarding complete response to NDA approvable letter
May 27, 1999	FDA	Orion´s response was considered a complete class 2 response to FDA´s action letter Therefore, the user fee goal date is October 19, 1999.
June 4, 1999	FDA / T. Wheelous	Request by reviewing statistician
June 10, 1999	Orion / Target	Information requested on 4 June was sent to FDA
July 2, 1999	FDA /R. Tresley	Request for additional information
July 6, 1999	FDA / T. Wheelous	Clarification of term requested
July 15, 1999	Orion / Target	Information requested on 2 June was submitted
July 16, 1999	FDA / Kun He	Request to clarify information contained in SAS Data Sets for Celomen study
July 21, 1999	FDA / Kun He	Additional data for Celomen study was requested

Date	Responsible	Subject
July 23, 1999	FDA / M. Sevka	Request for additional safety information different formulations
July 28, 1999	Orion / Target	Information requested on July 16 and July 21 was sent
July 30, 1999	Orion/Target	Response to questions raised by Dr. Sevka during July 23, concerning formulations was provided
August 13, 1999	FDA / M. Sevka	Questions regarding safety data submitted as part of the complete response
August 20, 1999	FDA / M. Sevka	Questions regarding safety data submitted as part of the complete response
September 3, 1999	FDA / M. Sevka	Additional request for safety information
September 9, 1999	Orion / Target	Response to questions made by Dr. Sevka August 13, August 20, September 3, 1999
October 4, 1999	Orion / Target	Investigator Financial Disclosure Information
October 5, 1999	Orion / Target	Full waiver for the submission of pediatric use information
October 7, 1999	FDA / T. Wheelous	Draft version of Comtan® labeling from FDA
October 8, 1999	Orion / Target	Revised labeling sent back to FDA
October 12, 1999	FDA + Orion + Novartis	Teleconference concerning the labeling
October 12, 1999	Orion / Target	Final Draft Labeling sent to FDA
October 18, 1999	Orion / Target	Authorization Letter to Novartis Pharmaceuticals
October 19, 1999	FDA	Approval Letter was issued

XII. ELIGIBILITY OF PATENT FOR EXTENSION

In the opinion of Applicant, the '194 Patent is eligible for an extension of the term for 416 days, and to thus expire on October 19, 2013. The length of the claimed extension of 416 days was determined by Applicant pursuant to 37 C.F.R. § 1.775, to be fourteen (14) years from the date of the FDA final approval, as described below:

A. Length of the Regulatory Review Period (37 C.F.R. § 1.775(c))

1. Period Pursuant to Paragraph (c)(1)

The period defined at 37 C.F.R. § 1.775(c)(1) began on November 29, 1991 (the date the IND became effective) and ended on January 2, 1998 (the date the NDA was filed). The (c)(1) period is thus 2,227 days.

2. Period Pursuant to Paragraph (c)(2)

The period defined at 37 C.F.R. § 1.775(c)(2) began on January 2, 1998 (the date the NDA was submitted pursuant to Section 505(b) of the FFDCA) and ended October 19, 1999 (the commercial marketing and use approval date). The (c)(2) period is thus 656 days.

The total (c)(1) and (c)(2) time period is thus 2,883 days.

B. Term of the Patent as Extended (37 C.F.R. § 1.775(d))

The term of the '194 Patent, as extended, was then calculated to expire on October 19, 2013, pursuant to 37 C.F.R. § 1.775(d).

1. (d)(1) Period (Days Subtracted from Regulatory Review Period)

The regulatory review period upon which the period of extension is calculated by subtracting, from the regulatory review period as determined in (c)(1) and (c)(2) of this section, the following:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) above which were on or before August 29, 1995, the issue date of the original patent.

The number of days in the period of the IND, effective on November 29, 1991, which were on or before August 29, 1995, the date the '194 Patent issued, is a period of 1,369 days. Therefore, 1,369 days are deducted from 2,227 days to equal 858 days.

The number of days in the period of the NDA, with the initial submission of NDA 20-796 on January 2, 1998, and approval on October 19, 1999, which were on or before August 29, 1995, the date the '194 Patent was issued, is a period of 0 days. Thus, 0 days are deducted to equal 656 days.

The total number of days after deduction is 1,514.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) during which the Applicant did not act with due diligence.

In the Applicant's opinion, marketing applicant acted with due diligence as defined at 35 U.S.C. § 156(d)(3) during the above calculated periods of paragraphs (c)(1) and (c)(2). Accordingly, zero days are subtracted from the regulatory review period.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section (ignoring half days).

There are 2,227 days in the period defined by paragraph (c)(1). The total deduction from 2,227 days pursuant to paragraphs (d)(1)(i) and (ii) of this section are 1,369, which equals 858 days. One half of 2,227 days, ignoring half days for purposes of subtraction, is 1,113.5 days. Subtracting 1,113.5 days from 2,883 results in a time period of 1,769.5 days.

Thus, the period determined according to paragraph (d)(1) is 1,769 days.

2. (d)(2) Date

The number of days determined in paragraph (d)(1), 1,769 days, added to the original term of the patent, *i.e.*, 17 years from the issue date (August 29, 1995), results in an extended patent expiration date of July 3, 2017.

3. (d)(3) Date

Fourteen years added to the October 19, 1999, the date of approval under the Federal Food, Drug and Cosmetic Act, yields an extended patent expiration date of October 19, 2013.

4. (d)(4) Date

Comparing the extended terms determined according to paragraphs (d)(2) and (d)(3), the earlier date is October 19, 2013.

5. (d)(5) Date

The original patent issued after September 24, 1984. Five years added to the original expiration date (August 29, 2012) of the patent is August 29, 2017.

By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other, the earlier date is October 19, 2013.

6. (d)(6) Date

The original patent was issued after September 24, 1984. Thus, this section thus does not apply.

XIII. ACKNOWLEDGMENT OF DUTY TO DISCLOSE

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is

material to the determination of entitlement to the term extension sought pursuant to 37 C.F.R. § 1.765.

XIV. APPLICATION FEE

Applicant submits herewith a check for $1,120.00 in payment of the fee set forth at 37 C.F.R. § 1.20(j).

The Commissioner is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment to Deposit Account No. 02-4800.

XV. CORRESPONDENCE ADDRESS

Please direct all correspondence and inquiries regarding this matter to:

Teresa Stanek Rea
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404
Tel: (703) 836-6620

XVI. DUPLICATE OF APPLICATION AND CERTIFICATION

Applicant encloses herewith a copy of the present application papers, and certifies that said copy is a duplicate of the application papers. For the convenience of the Senior Legal Advisor of the Patent Office, Applicant is also enclosing three (3) additional copies of the application.

XVII. DECLARATION

A Declaration pursuant to 37 C.F.R. § 1.740(b) is attached hereto.

In view of the foregoing, an extension of the term of the above-identified patent respectfully is requested.

Respectfully submitted

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: December 17, 1999

By: _____
Teresa Stanek Rea
Registration No. 30,427

Post Office Box 1404
Alexandria, VA 22313-1404
Tel: (703) 836-6620

EXHIBIT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-796

Orion Corporation
Attention: Robert Mc Cormack, Ph.D.
Vice-President, Regulatory Affairs
Target Research Associates
1801 East Second Street
Scotch Plains, N. J. 07076

OCT 19 1999

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated October 24, 1997, received January 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Comtan (entacapone) Tablets 200 mg.

We acknowledge receipt of your submissions dated:

April 16, 1999	May 24, 1999	May 25, 1999
July 15, 1999	July 28, 1999	July 30, 1999
September 9, 1999	October 5, 1999	

Your submission of April 16, 1999 constituted a complete response to our December 31, 1998 action letter.

This new drug application provides for the use of Comtan (entacapone) 200 mg tablets as an adjunct to levodopa / carbidopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (so-called "fluctuating" patients).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter. In particular, this approval applies to formulation 55.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-796." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated April 16, 1999 as requested in our December 31, 1998 action letter. This commitment is described below.

Pharmacology / Toxicology

We do not agree that you have provided evidence for saturation of absorption at doses of 100 mg/kg or higher in the mouse carcinogenicity study, and you have not demonstrated in a 3-month study that 100 mg/kg is approximately one half the maximum tolerated dose. As you have therefore failed to validate the existing study, it will be necessary for you to conduct a mouse carcinogenicity study during Phase 4. This study may be a repeat of the mouse bioassay or an alternative study such as the mouse p53 assay. If you choose an alternative mouse model, your justification for the choice and a protocol should be submitted for evaluation by the Executive Carcinogenicity Assessment Committee (ECAC). We also recommend that, if you choose to repeat the bioassay, you seek concurrence for dose selection from the ECAC. The dose selection studies should be initiated immediately, and the completed studies should be submitted as soon as possible.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. As an IND will not be required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

We note that in your October 5, 1999 submission, received October 6, 1999, you request a waiver of the pediatric study requirement in accordance with the provisions of 21 CFR 314. We will notify you within 120 days of receipt of your submission, February 3, 2000, whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. In the event that we deny your request for a waiver of the pediatric study requirements and, therefore, conclude that you must perform studies in (a subset of) the pediatric population, you may wish to qualify for pediatric exclusivity. In that case you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. If we do deny your waiver request, we recommend that you submit a Proposed Pediatric Study Request within 120 days from the date that we inform you of this denial. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

EXHIBIT 2

Assignment of Application for Patent

Whereas, Reijo Johannes Backstrom, Kalevi Evert Heinola, Erkki Juhani Honkanen, Seppo Kalevi Kaakkola, Pekka Juhani Kairisalo, Inge-Britt Yvonne Linden, Pekka Topias Mannisto, Erkki Kalme Olavi Nissinen, Pentti Ponto, Aino Kyllikki Pippuri

have invented certain new and useful improvements in NEW PHARMACOLOGICALLY ACTIVE COMPOUNDS, METHODS FOR THE PREPARATION THEREOF AND COMPOSITIONS CONTAINING THE SAME

(Title of Invention)

for which we are about to make application for

(He has made—or is about to make.)

Letters Patent of the United States of America:

And Whereas, Orion-yhtyma Oy

of Espoo, Finland

is desirous of acquiring an interest therein and in the Letters Patent to be obtained therefor from the United States;

Now Therefore, be it known by all whom it may concern, that for and in consideration of ONE Dollars ($ 1.00) and other valuable consideration to us in hand paid, the receipt of which is hereby acknowledged we have assigned, sold, and set over, and by these presents do assign, sell, and set over unto the said Orion-yhtyma Oy

~~for the territory of the United States of America, its territories, and dependencies,~~

† for the territory of the United States of America, and for all foreign countries

* the entire right, title, and interest in and to the said invention, as fully set forth and described in the specification prepared and executed by us on Nov. 16, 1987 19..... filed 19..., serial No....., preparatory to obtaining Letters Patent therefor; said invention, application and Letters Patent to be held and enjoyed by the said Orion-yhtyma-Oy for its own use and behoof, and for the use and behoof of its successors, assigns and legal representatives to the full end of the term for which said Letters Patent are granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

In Testimony Whereof, We hereunto set our hands and affix our seal s at Espoo, Finland State of..... this 16th day of November A. D. 19 87

Signed, sealed and delivered in the presence of—

Signatures of Witnesses

Signature(s) of Inventor(s)

2 _____

8 _____

9 _____

10 _____

11 _____

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RECORDED
PATENT & TRADEMARK OFFICE

NOV 27 1987

COMMISSIONER OF PATENTS

EXHIBIT 3

US005446194A

United States Patent [19]

Bäckström et al.

[11] Patent Number: 5,446,194

[45] Date of Patent: Aug. 29, 1995

[54] PHARMACOLOGICALLY ACTIVE CATECHOL DERIVATIVES

[75] Inventors: Reijo J. Bäckström, Helsinki; Kalevi E. Heinola, Järvempää ; Erkki J. Honkanen, Vantaa; Seppo K. Kaakkola, Helsinki; Pekka J. Kairisalo, Helsinki; Inge-Britt Y. Linden, Helsinki; Pekka I. Männistö, Helsinki; Erkki A. O. Nissinen, Espoo; Pentti Pohto, Helsinki; Aino K. Pippuri; Jarmo J. Pystynen, both of Espoo, all of Finland

[73] Assignee: Orion-yhtymä Oy, Espoo, Finland

[21] Appl. No.: 121,617

[22] Filed: Sep. 16, 1993

Related U.S. Application Data

[60] Division of Ser. No. 987,245, Dec. 7, 1992, Pat. No. 5,283,352, which is a continuation of Ser. No. 792,655, Nov. 15, 1991, abandoned, which is a division of Ser. No. 587,791, Sep. 25, 1990, Pat. No. 5,112,861, which is a division of Ser. No. 126,911, Nov. 27, 1987, Pat. No. 4,963,590.

[30] Foreign Application Priority Data

Nov. 28, 1986 [FI] Finland 864875
May 27, 1987 [GB] United Kingdom 8712437

[51] Int. Cl.[6] C07C 205/22; C07C 255/50

[52] U.S. Cl. 558/401; 558/404; 558/414; 564/166; 564/167; 564/169; 560/136

[58] Field of Search 558/401, 404, 414; 564/166, 167, 169; 560/136

[56] References Cited

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0149952	7/1985	European Pat. Off. .
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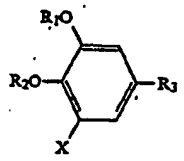
(List continued on next page.)

Primary Examiner—Jacqueline Haley

Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

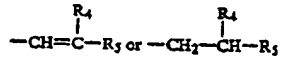
[57] ABSTRACT

A compound according to formula 1



1

wherein R_1 and R_2 independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents halogen nitro or cyano and R_3 represents



wherein R_4 represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R_5 represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof, and a pharmaceutically acceptable carrier therefor, as well as pharmaceutical compositions containing said compounds as COMT inhibitors.

4 Claims, 2 Drawing Sheets

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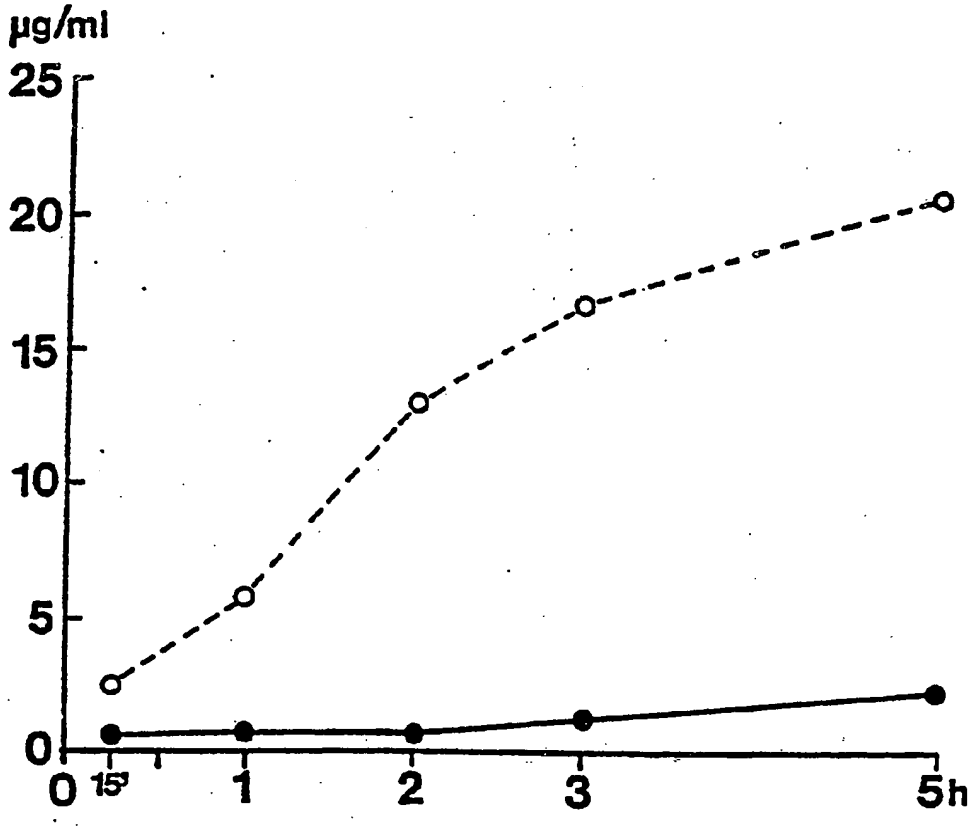


3 OMD CONCENTRATION IN SERUM

●—— Compound of Example 5

o----- Control

Fig. 1

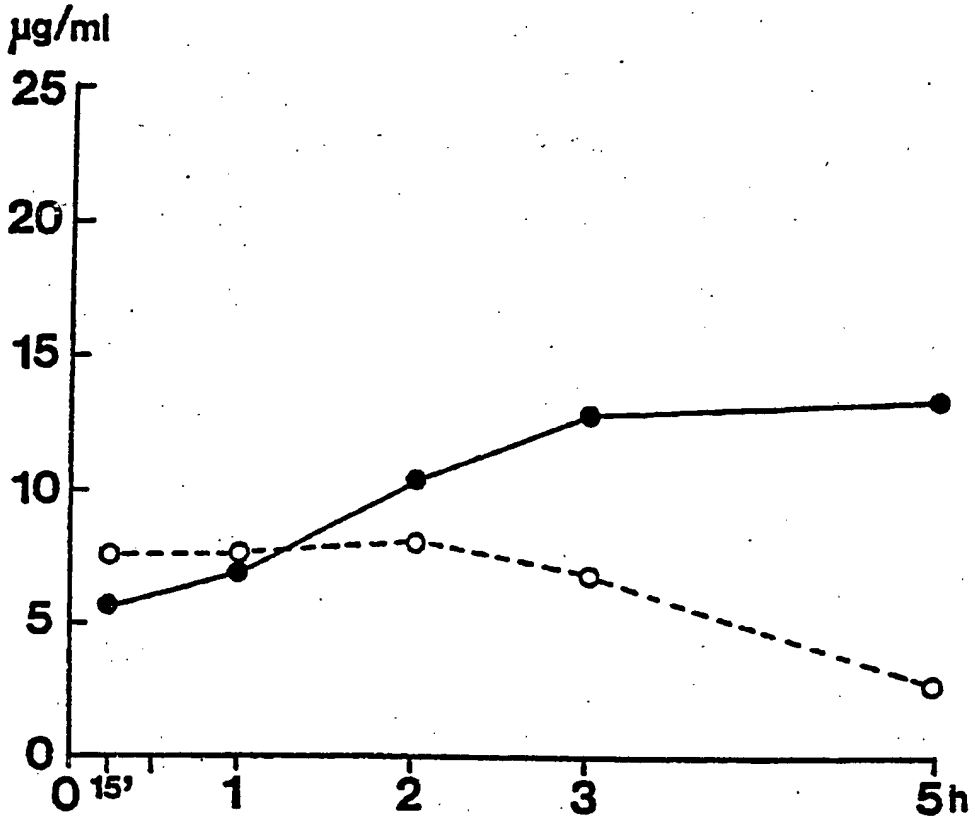
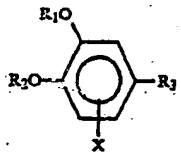

µg/ml
25
20
15
10
5
0
0
15'
1
2
3
5h
L-DOPA CONCENTRATION IN SERUM
Compound of Example 5
Control

Fig. 2

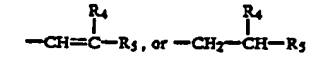
PHARMACOLOGICALLY ACTIVE CATECHOL DERIVATIVES

This application is a divisional of Application Ser. No. 07/987,245, filed Dec. 7, 1992, now U.S. Pat. No. 5,283,352, which is a continuation of Application Ser. No. 07/792,655, filed Nov. 15, 1991, now abandoned, which is a divisional of application Ser. No. 07/587,791, filed Sep. 25, 1990, now U.S. Pat. No. 5,112,861, which is a divisional of application Ser. No. 07/126,911, filed Nov. 27, 1987, now U.S. Pat. No. 4,963,590. The present invention relates to new pharmacologically active catechol derivatives according to formula I

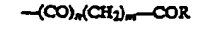


I

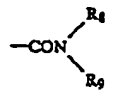
wherein R_1 and R_2 independently comprise hydrogen, alkyl, optionally substituted acyl or optionally substituted aroyl, lower alkylsulfonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group, X comprises electronegative substituent such as halogen, nitro, cyano, lower alkylsulfonyl, sulfonamido, trifluoromethyl, aldehyde or carboxyl and R_3 comprises hydrogen, halogen, substituted alkyl, hydroxyalkyl, nitro, cyano, optionally substituted amino, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidenecarbonyl or carboxyl group or a group selected from



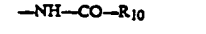
wherein R_4 comprises hydrogen, alkyl, amino, cyano, carboxyl or acyl and R_5 comprises hydrogen, amino, cyano, carboxyl, alkoxycarbonyl, carboxyalkenyl, nitro, acyl, hydroxyalkyl, carboxyalkyl, COZ, wherein Z is an optionally substitutted heterocyclic ring or one of following optionally substituted groups; carboxamido, carbamoyl, aroyl or heteroaryl or R_4 and R_5 together form a five to seven membered substituted cycloalkanone ring;



wherein n is 0–1, m is 0–7 and R comprises alkyl, hydroxy, carboxyalkyl, optionally substituted alkene, optionally substituted heterocyclic ring, alkoxy or substituted amino;



wherein R_8 and R_9 independently comprise hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or taken together form an optionally substituted piperidyl group;



wherein R_{10} comprises a substituted alkyl group.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the 3-LMD serum concentrations for the new compound and for a control compound which does not contain a COMT inhibitor.

FIG. 2 shows the levodopa serum concentrations after the same treatments.

The term "alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of up to 18 carbon atoms, preferably 1 to 8 carbon atoms, most preferably 1 to 4 carbon atoms. The term "lower alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of 1 to 7, preferably 1 to 4, most preferably i or 2 carbon atoms. Specific examples for the alkyl and lower alkyl residues, respectively, are methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, hexyl, octyl, decyl and dodecyl including the various branched chain isomers thereof.

The term "alkenyl" and "alkynyl" designate a hydrocarbon residue as defined above with respect to the term "alkyl" including at least one carbon to carbon double bond and carbon to carbon triple bond, respectively. The alkenyl and alkynyl residues may contain up to 12, preferably 1 to 8, most preferably 1 to 4 carbon atoms.

The term "acyl" as employed herein by itself or as part of another group refers to an alkylcarbonyl or alkenylcarbonyl group, the alkyl and alkenyl groups being defined above.

The term "aroyl" as used herein by itself or as part of another group refers to an arylcarbonyl group, the aryl group being a monocyclic or bicyclic group containing from 6 to 10 carbon atoms in the ring portion. Specific examples for aryl groups are phenyl, naphtyl and the like.

The term "lower alkylidene" refers to a chain containing from 2 to 8, preferably 2 to 4 carbon atoms. In a similar way the term "cycloalkylidene" refers to a cyclic hydrocarbon group containing 3 to 8, preferably 5 to 7 carbon atoms.

The term "alkoxy" as employed herein by itself or as part of another group includes an alkyl residue as defined above linked to an oxygen atom.

The term "cycloalkyl" includes saturated cyclic hydrocarbon groups containing 3 to 8, preferably 5 to 7 carbon atoms. Specific examples are the cyclopentyl, cyclohexyl, cycloheptyl and adamantyl groups.

The term "aralkyl" as employed herein refers to alkyl groups as defined above having an aryl substituent. A specific example is the benzyl group.

The term "halogen" as used herein refers to chlorine, bromine, fluorine or iodine, chlorine and bromine being preferred.

The term "optionally substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine or trifluoromethyl groups, alkoxy, aryl, alkyl-aryl, halogen-aryl, cycloalkyl, alkylcycloalkyl, hydroxy, alkylamino, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, or alkylthio substituents.

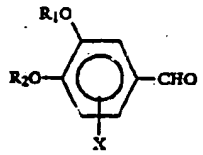
The "optionally substituted" groups may contain 1 to 3, preferably 1 or 2, most preferably I of the above mentioned substituents.

The term "heteroaroyl" or "heteroaryl" or "heteroalkyl" as employed herein refers to monocyclic-or bicy-

clic group containing 1 to 3, preferably 1 or 2 heteroatoms N and/or O and/or S. Specific examples are morfolinyl, piperidyl, piperidinyl, piperazinyl, pyridyl, pyrrolyl, quinolinyl and quinolyl.

The invention also relates to pharmaceutically acceptable salts of the present compounds.

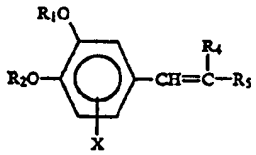
The present invention also relates to methods for the preparation of compounds of formula I. In accordance with the present invention compounds of formula I may be prepared for instance so, that an aldehyde of formula II


II

wherein R_1, R_2 and X are as defined above, is condensed in a base or acid catalyzed reaction with a compound of formula III


III

having an active methyl or methylene group and wherein R_4 and R_5 are as defined above, giving the compounds of formula Ia


Ia

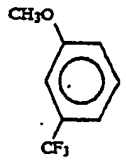
wherein R_4 and R_5 are as defined above and wherefrom the double bond optionally may be reduced to a single bond.

The compounds according to formula. II are also, in addition to being valuable medicines according to the present invention, new valuable intermediates for preparing other valuable products according to the invention.

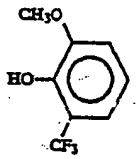
Compounds of formula II wherein x is a cyano group can be prepared from the corresponding compounds, wherein X is halogen, preferably bromine, by allowing these compounds to react with cuprous cyanide in a polar, aprotic solvent, such as pyridine, N-methylpyrrolidone or N,N-dialkylformamide at elevated temperature (100°–200° C.).

Alternatively the compounds of formula II, wherein X is a 5-cyano group can be prepared by formylation of 2,3-dihydroxybenzonitrile with hexamethylenetetramine.

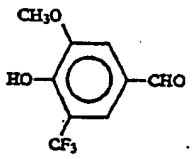
Compounds of formula II, wherein X is 5-trifluoromethyl can be prepared starting from 3-methoxytrifluoromethylbenzene of formula XIV


XIV

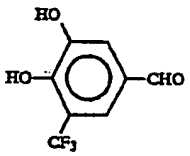
which compound is treated first with butyllithium and then with trimethylborate and further with performic acid to give the compound of formula XV


XV

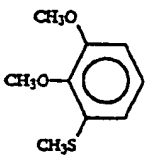
which compound is formylated with hexamethylenetetramine in trifluoroacetic acid to give a compound of formula XVI


XVI

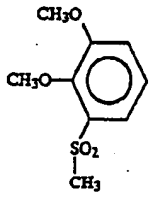
which compound is, if desired, demethylated for example with boron tribromide to give the compound of formula XVII


XVII

Compounds of formula II, wherein X comprises a 5-methylsulfonyl group, can be prepared from 2,3-dimethoxythioanisole of the formula XVIII

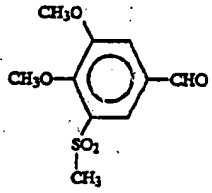

XVIII

which compound is treated first for example with peroxyacetic acid to give the corresponding sulfone of formula XIX



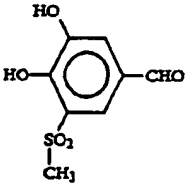
XIX

which compound is then formylated with hexamethylenetetramine in trifluoroacetic acid to give the compound of formula XX



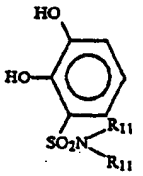
XX

which compound may be, if desired, demethylated (HSr or SBr_3) to give a compound of formula XXI



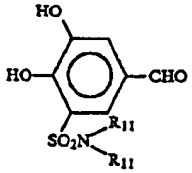
XXI

The compound of formula II, wherein X comprises sulfonamido, can be prepared by formylation of 2,3-dihydroxybenzenesulfonamide of formula XXII



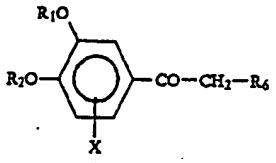
XXII

wherein R_{11} means hydrogen or alkyl, to give the compound of formula XXIII



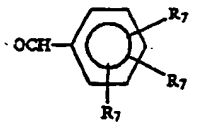
XXIII

Alternatively compounds of formula I according to the present invention can be prepared from a ketone of formula IV



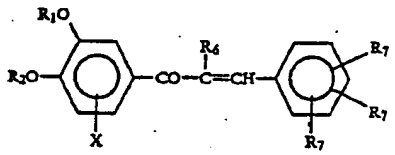
IV

wherein R_1, R_2, x are as defined above and R_6 comprises hydrogen or alkyl, by a condensation with an aldehyde of formula V



V

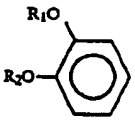
wherein R_7 comprises hydrogen, alkyl, alkoxy or dialkylamino to give the compounds of formula Ib



Ib

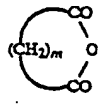
wherein R_1, R_2, X, R_6 and R_7 are as defined above.

Alternatively compounds of formula I, wherein R_3 comprises a substituted alkyl group can be prepared by Friedel-Craft's reaction from a compound of formula VI



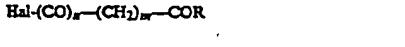
VI

wherein R_1 and R_2 are as defined above by allowing the compound of the formula VI to react in the presence of aluminium chloride either with a cyclic acid anhydride of formula VII



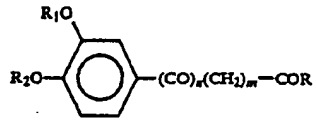
VII

wherein m is 1–7 or alternatively with a dicarboxylic acid ester chloride of formula VIII



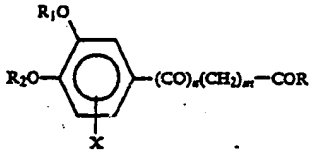
VIII

wherein m is 0–7 and n is 0–1 and R is as defined above and Hal is a halogen atom, to give the compounds of formula IX



IX

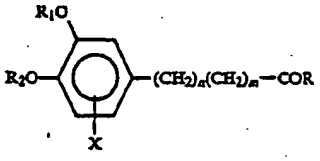
wherein the aromatic ring will be substituted with the group X to give the compounds of formula Ic



Ic

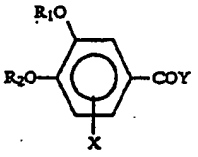
wherein R, R_1, R_2 and X are as defined above.

In the compounds of formula Ic the carbonyl group can be reduced to a methylene group by conventional methods (Clemmensen and Wolff-Kischner reduction) to give compounds of formula Id



Id

The compounds according to the present invention, wherein R_3 comprises a substituted carbamido group, can be prepared by allowing an activated benzoic acid derivative of formula X

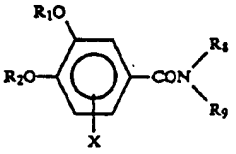


X

wherein R_1, R_2 and X are as defined above and Y comprises halogen or some other activated group to react with an amine of formula XI

XI

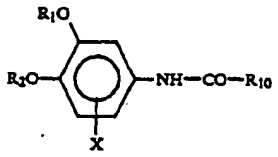
wherein R_8 and R_9 are as defined above to give compounds of formula Ie



Ie

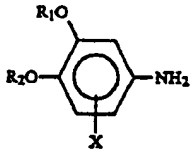
wherein R_1, R_2, X, R_8 and R_9 are as defined above.

The compounds of formula I, wherein R_3 is an acylated amino group having formula If



If

wherein R_1, R_2, X and R_{10} are as defined above can be prepared by allowing an aniline derivative of formula XII



XII

wherein R_1, R_2 and X are as defined above, to react with an activated carboxylic acid derivative of formula XIII

XIII

wherein Y and R_{10} are as defined above.

The invention relates to compositions where the compounds of formula I may be used as the active medicine. The compositions may contain the compounds of formula I alone or combined with some other medicines. For the treatment of Parkinson's disease the compounds according to formula I are given with levodopa, each in its own composition or combined in one composition. Also peripheral dopa decarboxylase (DDC) inhibitors, such as carbidopa or benserazide may be present, even though they are not obligatory.

The compounds according to this invention may be given in different dosage forms for administering in any suitable enteral or parenteral way. The dosage forms, like tablets, pills, injection liquids etc may be manufactured by the known principles in the art. One can use any pharmaceutically accepted additives, lubricants, fillers etc to modify different properties of the dosage forms.

Catechol-0-methyltransferase (COMT) catalyzes the transfer of the methyl group from S-adenosyl-n-methionine to a number of compounds with catechol structures. This enzyme is important in the extraneuronal inactivation of catecholamines and drugs with catechol structures. COMT is one of the most important enzymes involved in the metabolism of catecholamines. It is present in most tissues, both in the periphery and the central nervous system. The highest activities are found in the liver, intestine and kidney. COMT probably is present in soluble and membrane bound forms. The exact character of the two forms has not been established.

In Parkinson's disease the dopaminergic neurones, primarily the nigrostriatal neurones, are damaged, gausing dopamine deficiency in the cerebral basal ganglia. This deficiency can be compensated by levodopa which is converted to dopamine in the central nervous system under the influence of DDC.

Today, levodopa treatment is almost invariably supplemented with a peripheral DDC inhibitor to inhibit too early dopamine formation and thereby to increase

the cerebral levodopa concentration and to decrease the peripheral side effects of dopamine.

In addition to DDC, COMT metabolizes levodopa, converting it to 3-0-methyldopa (3-OMD). 3-OMD readily penetrates the blood-brain barrier via an active transport system. Alone it is therapeutically ineffective and detrimental when competing with levodopa. 3-OMD is accumulated in tissues because of its long half-life (ca. 15 h) compared to levodopa (ca. 1 h). The high activity of COMT clearly correlates with the poor efficacy of levodopa despite the presence of peripheral DDC inhibitor.

In addition to monoamine oxidase (MAO), COMT is a major enzyme participating in the amine metabolism. By inhibiting the metabolism of endogenous amines (dopamine, noradrenaline, adrenaline) in the brain the COMT inhibitors decrease decomposition of these compounds. Thus they may be useful in the treatment of depression.

By inhibiting peripheral COMT effectively, COMT inhibitors direct the metabolic route of levodopa towards decarboxylation, forming thereby more dopamine which is important in the treatment of hypertension and heart failure.

It has been unexpectedly observed that the compounds according to the invention are extremely effective COMT inhibitors. They open up new, previously unknown possibilities in the treatment of Parkinson's disease. In addition the new compounds may be useful also in the treatment of depression and heart failure as well as hypertension.

The new COMT inhibitors, which inhibit formation of 3-OMD, may decrease the adverse effects of long-term use of levodopa. Furthermore, levodopa doses can be reduced. It has been shown that the dose of levodopa can be reduced by half or to one-third of the dose used without COMT inhibitor. Since dosage of levodopa is individual, it is difficult to give any absolute dosage, but daily doses as low as 25–50 mg have been considered sufficient to start with.

A preliminary clinical trial on n-butyl gallate, a known COMT inhibitor, showed patients with Parkinson's disease clearly to benefit of n-butyl gallate. The study was, however, discontinued because of the too high toxicity of n-butyl gallate.

The COMT inhibitory efficacy of the compounds according to the invention was tested using the following experimental procedures.

Determination of COMT activity in vitro

The in vitro activity of COMT was determined in enzyme preparations isolated from the brain and liver of female Han:WIST rats, weight ca. 100 g. The rats were killed by carbon dioxide, and the tissues were removed and stored at −80° C. until determination of enzyme activity.

The enzyme preparation was prepared by homogenizing the tissues in 10 mM phosphate buffer, pH 7.4, (1:10 weight g/ml) which contained 0.5 mM dithiotreitol. The homogenate was centrifuged 15000 x G for 20 min. The supernatant was recentrifuged 100000 x G for 60 min. All procedures were done at +4° C. The supernatant of the last centrifugation (100000 x G) was used to determine the activity of soluble COMT enzyme.

Determination of IC_{50} was performed by measuring the COMT activity in several drug concentrations of the reaction mixture which contained the enzyme preparation, 0.4 mM dihydroxybenzoic acid (substrate), 5 mM magnesium chloride, 0.2 mM S-adenosyl-L-methionine and COMT inhibitor in 0.1 M phosphate buffer, pH 7.4.No COMT inhibitor was added to the control. The mixture was incubated for 30 min at 37° C. whereafter the reaction was stopped by perchloric acid and the precipitated proteins were removed by centrifugation (4000 x G for 10 min). The activity of the enzyme was measured by determining the concentration of 3-methoxy-4-hydroxybenzoic acid formed from the substrate of COMT (dihydroxybenzoic acid) by HPLC using an electrochemical detector. Chromatography was performed by injecting 20 µl of the sample in a 4.6 mm×150 mm Spherisorb ODS column (particle size 5 µm). The reaction products were eluted from the column with 20% methanol containing 0.1 M phosphate, 20 mM citric acid and 0.15 mM EDTA, pH 3.2, at a flow rate of 1.5 ml/min. The electrochemical detector was set to 0.9 V against an Ag/AgCl electrode. The concentration of the reaction product, 3-methoxy-4-hydroxybenzoic acid, was compared with the control samples and the samples containing COMT inhibitor. The IC50 value is the concentration which causes a 50% decrease in COMT activity.

Effect of COMT inhibitors in vivo

Male Han:WIST rats, weight 200–250 g, were used in the experiment. The control group was given 50 mg/kg carbidopa 30 min before levodopa (50 mg/kg). The test group was also given carbidopa 50 mg/kg 30 min before levodopa+COMT inhibitor. The drugs were administered orally.

Sampling

About 0.5 ml of blood was drawn from the tail artery. The sample was allowed to coagulate in ice. Thereafter the sample was centrifuged and serum separated. Serum was stored at −80° C. until determination of concentrations of levodopa and its metabolite 3-OMD.

Determination of levodopa and 3-OMD serum concentrations

To serum (e.g. 100 µl), an equal volume of 0.4 M perchloric acid, 0.1% sodium sulphate, 0.01% EDTA, which contained dihydroxybenzylamine as internal standard, were added. The sample was mixed and kept in ice, whereafter the proteins were removed by centrifugation (4000 x G for 10 min.) and the concentrations of levodopa and 3-OMD were determined by HPLC using an electrochemical detector. The compounds were separated in a 4.6 mm×150 mm Ultrasphere ODS column in an eluent containing 4% acetonitrile, 0.1 M phosphate buffer, 20 mM citric acid, 0.15 mM EDTA, 2 mM octylsulphonic acid and 0.2% tetrahydropholan, pH 2.8. The flow rate was 2 ml/min. The electrochemical detector was set to +0.8 V against an Ag/AgCl electrode. The concentrations of the test compounds were determined by comparing the heights of the peaks with that of the internal standard. The ratio was used to calculate the serum concentrations of levodopa and 3-OMD in control rats and those given COMT inhibitor.

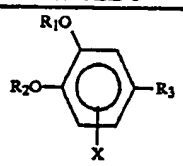
Results

The best COMT inhibitors according to the invention were more than thousand times more potent in vitro than the most potent known reference compound U-0521 (Table I). Also the orally administered COMT

inhibitors were shown to inhibit the formation of serum 3-OMD significantly more than U-0521 (Table II). The reference compound U-0521 furthermore penetrated the blood-brain barrier and inhibited the thyrosine hydroxylase activity thereby blocking the biosynthesis of vitally important catecholamines. In contrast the compounds according to the invention are COMT specific and they do not significantly penetrate the blood-brain barrier.

Results in vitro

TABLE 1



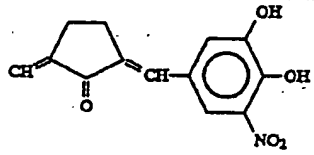
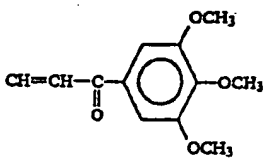
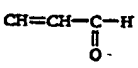
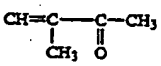
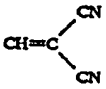
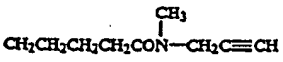
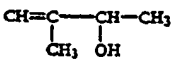
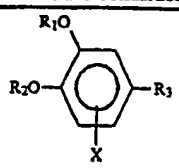
Example compound	R_1	R_2	X	R_3	COMT-INHIBITION IN BRAIN TISSUE (IC50(nM)
79	H	H	5-NO_2		3
11	H	H	5-NO_2		5
8	H	H	5-NO_2		6
6	H	H	5-NO_2		12
110	H	H	5-NO_2	NO_2	12
109	H	H	5-NO_2		16
130	$CH_3(CH_2)_2C(=O)$	H	5-NO_2	NO_2	18
5	H	H	5-NO_2		20
27	H	H	5-NO_2		20
16	H	H	5-NO_2		23
111	H	H	5-NO_2		24
113	H	H	5-NO_2	—Cl	25
112	H	H	5-NO_2	—CN	30
28	H	H	5-NO_2		27

TABLE 1-continued



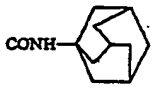
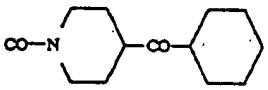
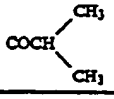
Example compound	R_1	R_2	X	R_3	COMT-INHIBITION IN BRAIN TISSUE (IC50(nM)
26	H	H	5-NO_2	$CH_2CH_2CH_2CH_2CONH-CH(CH_3)_2$	33
3	H	H	5-NO_2	CH=CH—COOH	37
128	$CH_3CH_2C(=O)$	$CH_3CH_2C(=O)$	5-NO_2	NO_2	60
127	$CH_3—C(=O)$	$CH_3—C(=O)$	5-NO_2	75	
24	H	H	5-NO_2	$CH_2CH_2CH_2CH_2COOH$	90
109	H	H	5-NO_2	—H	140
131	$(CH_3)_3C—C(=O)$	H	5-NO_2	NO_2	220
41	H	H	6-NO_2	$CH_2CH_2CH_2CH_2COOH$	380
54	H	H	5-Cl		400
67	CH_3CO	CH_3CO	6-NO_2		750
U-0521	H	H	5-H		6000

TABLE 2

		In vivo results	
		3-OMD concentration % of control	
Oral dose	Compound	1 h	5 h
3 mg/kg	Example 110	−97	−80
4.3 mg/kg	Example 127	−67	−76
4.7 mg/kg	Example 128	−70	−77
4.3 mg/kg	Example 131	−92	−83
4.1 mg/kg	Example 130	−98	−92
30 mg/kg	Example 19	−99	−76
30 mg/kg	Example 111	−100	−65
30 mg/kg	Example 5	−96	−89
30 mg/kg	Example 6	−84	−49
30 mg/kg	Example 11	−63	−26
30 mg/kg	Example 8	−58	−34
100 mg/kg	Example 24	−86	−41
100 mg/kg	U−0521	−34	−14

The results indicate that the compounds according to the invention are even more than thousand times more potent in vitro (Table 1) than the reference coumpound (U-0521). The orally administered new compounds inhibit COMT also in vivo significantly better than the reference compound, which is reflected as decreased serum 3-OMD concentration (Table 2). The reference compound U-0521 furthermore penetrates the blood-brain barrier and nonspecifically inhibits thyrosine hydroxylase which is essential for the biosynthesis of catecholamines.

FIG. 1 shows the 3-OMD serum concentrations for the new compound (e.g. according to example 5) and for the control compound which does not contain COMT inhibitor. The experimental design is the same as for the in vivo experiments above. FIG. 2 shows the levodopa serum concentrations after the same treatments. These figures show that the compounds according to the invention increase the bioavailability of levodopa and decrease the level of the harmful metabolite 3-OMD. The change observed in serum is reflected in the brain concentrations of 3-OMD and levodopa.

Specificity of COMT inhibition

The new compounds are specifically comt inhibitors and not inhibitors of other essential enzymes. This was

shown in in vitro experiments which were performed as described above.

Compound	IC_{50} (nM) COMT	TH	DBH	DDC	MAO-A	MAO-B
Example 87	3	38.000	>50.000	>50.000	>50.000	>50.000
Example 11	5	18.000	>50.000	>50.000	>50.000	>50.000
Example 8	6	21.000	>50.000	>50.000	>50.000	>50.000
Example 6	12	50.000	>50.000	>50.000	>50.000	>50.000
Example 110	12	14.000	>50.000	>50.000	>50.000	>50.000
Example 19	16	17.500	>50.000	>50.000	>50.000	>50.000
Example 5	20	21.000	>50.000	>50.000	>50.000	>50.000
Example 111	24	50.000	>50.000	>50.000	>50.000	>50.000
U-0521	6000	24.000	>50.000	>50.000	>50.000	>50.000

TH=Thyrosine hydroxylase, DBH=Dopamine-β-hydroxylase MAO-A and -B=Monoamine oxidase-A and -B.

The COMT inhibitors according to the invention are extremely specific. They inhibit COMT effectively at low concentrations, while inhibition of other enzymes involved in the metabolism of catecholamines requires a 1000–10000 times higher concentration. The difference between the inhibition of TH and COMT in the reference compound U-0521 is only 4-fold.

IC_{50} is the concentration which inhibits 50% of the enzyme activity.

Toxicity

The new COMT inhibitors are non-toxic. For instance, the LD_{50} of 3-(3,4-dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (Example 11) given as an oral suspension to rats, was over 2500 mg/kg.

EXAMPLE 1

3-Nitro-5-[2-(4-pyridyl)vinyl]catechol

A solution containing 2.0 g (0.011 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.23 g (0,024 mole) of 4-picoline in 9.0 ml of acetic anhydride was refluxed for 1 h. About 15 ml of isopropanol was then added and the solution was cooled to 0° C. where upon the diacetyl-derivative of the desired product crystallized. After filtration the product was suspended in 100 ml of 0.5 N hydrochloric acid and refluxed for 1.5 h. After cooling the precipitate was filtered, washed with water and acetone and dried. Yield 1.89 g (67%), m.p. above 350° C.

EXAMPLE 2

3-Nitro-5-[2-(4-quinolyl)vinyl]catechol

The same procedure described in Example 1 was repeated using 2.0 g (0.011 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde and 3.44 g (0.024 mole) of 4-quinaldine. Yield 1.7 g (50%), m.p. 250° C. (decomp.).

EXAMPLE 3

4-Hydroxy-3-methoxy-5-nitrocinnamic acid

A solution of 1.0 g of 5-nitrovanillin and 4.0 g of malonic acid in 10 ml of pyridine was heated for 50 h at 80° C. The reaction mixture was diluted with water, acidified with hydrochloric acid, filtered, washed with water and dried. Yield 0.44 g (36%). The ^{1}H-NMR spectrum was in accordance with the structure alleged.

EXAMPLE 4

3,4-Dihydroxy-5,ω-dinitrostyrene

A solution containing 3.66 g (0.02 mole) of 3,4-dihydroxy- 5-nitrobenzaldehyde, 3.66 g (0.06 mole) of nitromethane and 3.31 g of ammonium acetate in 10 ml of abs. ethanol was refluxed for 6 h. Water was added to the reaction mixture. The mixture was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride extract was washed with water and the solvent was evaporated in vacuo. The residue was crystallized from isopropanol, yield 1.9 g (40%), m.p. 258°–260° C.

EXAMPLE 5

3,4-Dihydroxy-5-nitro-ω,ω-dicyanostyrene

The same procedure described in Example 4 was repeated using 3.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 3.0 g of malonodinitrile. The product was crystallized from methanol-water, yield 1.9 g (50%), m.p. 205°–209° C.

EXAMPLE 6

4-(3,4-Dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-one

A solution containing 0.5 g of 3,4-dihydroxy-5-nitrobenzaldehyde in 2.0 ml of butanone was saturated with gaseous hydrogen chloride. After standing over night ether was added to the solution and it was filtered. The product was crystallized from isopropanol, yield 0.2 g (30%), m.p. 139°–141° C.

EXAMPLE 7

3-(3,4-Dihydroxy-5-nitrobenzylidene)-2,4-pentanedione

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.00 g of 2,4-pentanedione in 10 ml of tetrahydrofuran was saturated with gaseous hydrogen chloride. After standing over night at 5° C. the product was filtered and washed with ether. Yield 1.2 g (50%), m.p. 175°–178° C.

EXAMPLE 8

3-(3,4-Dihydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 0.55 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.36 g of acetophenone in 10 ml of methanol was saturated with gaseous hydrogen chloride. After standing over night at 5° C. the product was filtered and washed with methanol. Yield 0.55 g (68%), m.p. 192°–195° C.

EXAMPLE 9

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methoxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.8 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.5 g of 4'-methoxyacetophenone in 20 ml of tetrahydrofuran. Yield 1.88 g (60 m.p. 222°–228° C.

EXAMPLE 10

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.8 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 18 g of 3',4'-dimethoxyacetophenone in 20 ml of methanol. Yield 1.7 g (50%), m.p. 206°–208° C.

EXAMPLE 11

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 0.55 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.63 g of 3',4',5'-trimethoxyacetophenone Yield 0.50 g (44%), m p 213°–216° C.

EXAMPLE 12

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(2-hydroxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.74 g of 2'-hydroxyacetophenone. Yield 0.2 g (12%), m.p. 231°–234° C.

EXAMPLE 13

3-(3,4-Diacetoxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 1.0 g of the product obtained in Example 8 in 5.0 ml of acetic anhydride was refluxed for 2 h. After cooling the product was filtered and washed with ether. Yield 0.73 g (68%), m.p. 183°–185° C.

EXAMPLE 14

3-(3,4-Dibenzoyloxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

1.0 g of the product obtained in Example 8 and 2.0 ml of benzoylchloride were dissolved in 5 ml of tetrahydrofuran. Tetrahydrofuran was distilled off to a great extent and the residue was refluxed for 2 h. After cooling ether was added to the mixture and the product was filtered and triturated with ethylmethylketone. Yield 0.50 g (29%), m.p. 206°–210° C.

EXAMPLE 15

3-(3-Pivaloyloxy-4-hydroxy-5-nitrophenyl)-1-phenyl-prop-2-en-1-one

1.0 g of the product obtained in Example 8 was dissolved in 5 ml of tetrahydrofuran, 4.7 ml of pivaloyl chloride was added and the mixture was refluxed for 16 h. The solvent was evaporated in vacuo and the residue was purified in a silicagel column by using toluene-acetic acid-dioxane (18:1:1) mixture as an eluent. The product was crystallized from ether, m.p. 148°–150° C.

EXAMPLE 16

4-(3,4-Dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-ol

1.8 g of the product obtained in Example 6 was dissolved in 20 ml of 1N NaOH-solution and 4.0 g of sodium borohydride in small amount of water was added. The mixture was stirred over night at room temperature, acidified with hydrochloric acid and extracted with ether. The solvent was evaporated in vacuo and the residue purified in a silica gel column by using toluene-acetic acid dioxane (18:1:1). The product was crystallized from dichloromethane petroleum ether. Yield 0.80 g (44%), m.p. 102°–104° C.

EXAMPLE 17

7-(3,4-Dihydroxy-5-nitrobenzylidene)-8-ketononanoic acid

The procedure described in Example 9 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.72 g of 8-ketononanoic acid. Yield 1.85 g (55%), yellow viscous oil.

EXAMPLE 18

4'-Hydroxy-3'-methoxy-5'-nitroacetophenone

To a solution containing 40 ml of nitric acid (d-1.41) and 40 ml of water was gradually added while cooling (below 7° C.) and stirring 25.0 g of 4'-hydroxy-3'-methoxyacetophenone. After stirring for 0.5 h at 0° C. the product was filtered, washed first with diluted nitric acid (1:1) and then with water. Yield 24.0 g (75%). The ^{1}H-NMR-spectrum of the product was in accordance with the structure alleged.

EXAMPLE 19

3,4,-Dihydroxy-5'-nitroacetophenone

A solution containing 19.9 g of the product obtained in Example 18 in 200 ml of acetic acid and 200 ml of 48% hydrobromic acid was refluxed for 5 h. 500 ml of a saturated solution of sodium sulfate was added to the reaction mixture and the same was let stand overnight at 5° C. The solution was extracted with ether. The ether phase was washed with 200 ml of water, dried and the solvent evaporated in vacuo. The residue was crystallized from isopropanol. Yield 10.2 g (55 m.p. 155°–159° C.

EXAMPLE 20

1-(3,4-Dihydroxy-5-nitrophenyl)-3-(4-dimethylaminophenyl)-prop-2-en-1-one

A solution containing 0.5 g of the product obtained in Example i9 and 0.38 g of 4-dimethylaminobenzaldehyde in 5 ml of methanol was saturated with gaseous hydrogen chloride. The solution was refluxed for 1 h. After cooling the product was filtered and washed with methanol. Yield 0.26 g (70%), decomp. on heating.

EXAMPLE 21

5-(4-Benzyloxy-3-methoxyphenyl)-2,4-pentadienoic acid

To a solution containing 260 g of 4-benzyloxy-3-methoxybenzaldehyde and 200 ml of ethyl crotonate in 1200 ml of N-methylpyrrolidone was gradually added while stirring and cooling at 0° C. 149.6 g of potassium tert.-butoxide. The solution was stirred for 0.5 h after which 200ml of 10 N NaOH-solution was added and

stirred for 0.5 h more at 0° C. The reaction mixture was added to a mixture of hydrochloric acid and ice. The semisolid product was separated and used without purification to the next step.

EXAMPLE 22

(4-Hydroxy-3-methoxyphenyl)pentanoic acid

The raw product obtained in Example 21 was dissolved in 500 ml of N,N-dimethylformamide and 22 g of 10% palladium on charcoal catalyst was added. The mixture was hydrogenated at 60° C. and normal pressure until the theoretical amount (3 mole) of hydrogen was consumed. After filtering the solvent was evaporated in vacuo to a great extent and the residue was dissolved in 1 l of dichloromethane and washed with 2 l of water. The product was extracted with 1.5 l of saturated $NaHCO_3$-solution. After acidification of the aqueous phase with hydrochloric acid the product was extracted with 1 l of dichloromethane. The solvent was distilled off in vacuo and the semisolid residue (180 g) was used to the next step.

EXAMPLE 23

5-(4-Hydroxy-3-methoxy-5-nitrophenyl)pentanoic acid

The above product (180 g) was dissolved in 1 l of dichloromethane and 820 ml of 1 molar HNO_3-dichloromethane solution was added gradually while stirring and cooling (0°-5° C.). The solution was stirred for 10 min more at 0° C. after which water was added. The organic phase was separated and washed with water. The solvent was evaporated in vacuo and the semisolid residue was used as such to the next step.

EXAMPLE 24

5-(3,4-Dihydroxy-5-nitrophenyl)pentanoic acid

The above product obtained in Example 23 was dissolved in a mixture containing 500 ml of acetic acid and 500 ml of 48% hydrobromic acid and refluxed for 4 h. 1 l of saturated Na_2SO_4-solution was added to the reaction mixture and the solution was allowed to stand over night at 5° C. The product crystallized was filtered and washed with 50% acetic acid. This product was recrystallized from ethyl acetate. Yield 32 g (16%), m.p. 135°-138° C.

EXAMPLE 25

1-Benzyl-4-[5-(3,4-dihydroxy-5-nitrophenyl)pentanoyl-piperazine hydrochloride

A solution containing 3.0 g of the product obtained in Example 24 in 18 ml of thionyl chloride was refluxed for 10 min. The excess of thionyl chloride was evaporated in vacuo and the acid chloride formed was dissolved in 20 ml of dichloromethane. To this solution 2.1 g of 1-benzylpiperazine in 20 ml of dichloromethane was added with stirring and stirred for 0.5 h more. Ether was added to the reaction mixture and the crystals were filtered. Yield 3.55 g (73%), m.p. 85°-89° C.

EXAMPLE 26

N-Isopropyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

A solution containing 0.5 g of the product obtained in Example 24 in 2.5 ml of thionyl chloride was refluxed for 10 min. The excess of thionyl chloride was evaporated in vacuo and the residue dissolved in 25 ml of dichloromethane. To this solution 0.47 g of isopropylamine was added and the mixture was Stirred for 1 h at 20° C. Dichloromethane phase was washed with 1 N hydrochloric acid and evaporated in vacuo. The residue was crystallized from tohuene. Yield 0.44 g (75%), m.p. 113°-115° C.

EXAMPLE 27

N-Methyl (-N-propargyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

The procedure described in Example 26 was repeated using 0.5 g of methyl propargylamine instead of isopropylamine. Yield 0.5 g (83%), mp. 133°-135° C.

EXAMPLE 28

N-(1-Adamantyl)-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

The procedure described in Example 26 was repeated using 1.5 g of 1-aminoadamantane instead of isopropylamine. Yield 0.61 g (80%), m.p. 157°-160° C.

EXAMPLE 29

Tetradecyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoate

The procedure described in Example 26 was repeated using 1.26 g of 1-tetradecanol instead of isopropylamine. The reaction mixture was washed with water and the solvent evaporated in vacuo. Yield 0.44 g (50%), m.p. 46°-47° C.

EXAMPLE 30

Tetradecyl-5-(3,4-diacetoxy-5-nitrophenyl)pentanoate

A solution containing 0.1 g of the product obtained in Example 29 in 2 ml of acetic anhydride was refluxed for 20 min. The solvent was evaporated in vacuo and the residue crystallized from petroleum ether (b.p. 40° C.), m.p. 52°-54° C.

EXAMPLE 31

Tetradecyl-5-(4-hydroxy-3-pivaloyloxy-5-nitrophenyl) pentanoate

The procedure described in Example 30 was repeated using 2 ml of pivaloyl chloride instead of acetic anhydride. The product was a viscous oil.

EXAMPLE 32

5-(3,4-Dimethoxy-5-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 10.0 g of 3,4-dimethoxy-5-chlorobenzaldehyde and 8.3 ml of ethyl crotonate in 65 ml of N-methylpyrrolidone 6.7 g of potassium tert.-butoxide was added with stirring. The solution was stirred for 0.5 h more at 20° C. and the solution was poured then to a mixture of ice and hydrochloric acid and extracted with ether. The ether extract was washed with water and extracted then with $NaHCO_3$-solution. The aqueous phase was acidified with hydrochloric acid and the semisolid product was separated and washed with water. Yield 7.3 g (55%).

EXAMPLE 33

5-(3,4-Dimethoxy-5-chlorophenyl)pentanoic acid

A solution containing 6.2 g of the above product obtained in Example 32 was dissolved in a mixture of 30 ml of acetic acid and 3 ml of conc. hydrochloric acid. Palladium on charcoal catalyst (10% Pd) was added

and the mixture was hydrogenated at normal pressure and room temperature. After filteration the solvents were evaporated in vacuo. Yield 3.2 g (55%), a viscous oil.

EXAMPLE 34

5-(3,4-Dihydroxy-5-chlorophenyl)pentanoic acid

A solution containing 3.2 g of the above product in 8 ml of acetic acid and 10 ml of 48% hydrobromic acid was refluxed for 3 h. A saturated solution of Na_2SO_4 in water was added to the reaction mixture. The crystallized product was filtered, washed with water and recrystallized from toluene, m.p. 99°–101° C.

EXAMPLE 35

5-(3,4-Dimethoxy-6-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 10.0 g 3,4 dimethoxy-6-chlorobenzaldehyde and 8 ml of ethyl crotonate in 60 ml of N-methylpyrrolidone 6.0 g of potassium tert.-butoxide was added while stirring. The solution was stirred for 0.5 h more at 20° C. and poured then to a mixture of ice and hydrochloric acid. The solution was extracted with ether. The ether solution was washed with water and extracted with 2.5 N NaOH-solution. The aqueous phase was acidified with hydrochloric acid and the semisolid product was separated. Yield 10.8 g (81%).

EXAMPLE 36

5-(3,4-Dihydroxy-6-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 0.54 g of the product obtained in Example 35 in 6 ml dichloromethane 6 ml of 1 molar boron tribromide-dichloromethane solution was added and stirred for 24 h at 20° C. The solvent was evaporated in vacuo and 2 N hydrochloric acid was added to the residue. The product was filtered and washed with water. Recrystallization from isopropanol-water yielded 0.22 g (46%) of the product desired, m.p. 203—206° C.

EXAMPLE 37

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methylphenyl)-prop-2-en-1-one

A solution containing 5.49 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 5.37 g of 4'-methylacetophenone in 50 ml of tetrahydrofuran was added a catalytic amount of gaseous hydrogen chloride and refluxed for 4.5 h. The solvent was evaporated in vacuo and the residue crystallized from ether-petroleum-ether, yield 1.85 g (21%), m.p. 184°–186° C.

EXAMPLE 38

5-(3,4-Dimethoxyphenyl)-5-ketopentanoic acid

A solution containing 36 g of veratrole and 30 g glutaric anhydride in 120 ml of nitrobenzene was gradually added while stirring and cooling at 0° C. to a mixture of 72 g of anhydrous aluminium chloride and 240 ml of nitrobenzene. The mixture was stirred for 1 h at 0° C. and then for 18 h at 20° C. Ice and hydrochloric acid were added to the reaction mixture. Nitrobenzene layer was separated and to this ethyl acetate was added whereupon the product crystallized. After filtering the crystals were washed with ethyl acetate. Yield 42.3 g (64%).

EXAMPLE 39

5-(3,4-Dimethoxyphenyl)pentanoic acid

A mixture containing 37.6 g of the product obtained in Example 38 and 64 g of zinc turnings (treated with a solution of $HgCl_2$), 55 ml of toluene and 220 ml of cone. hydrochloric acid was refluxed for 1 h. Toluene phase was separated and evaporated in vacuo. The residue was crystallized from toluene-petroleum ether, yield 11.5 g (32%).

EXAMPLE 40

5-(3,4-Dimethoxy-6-nitrophenyl)pentanoic acid

15.0 g of product described in Example 39 was gradually added to 75 ml of nitric acid (d-1.41) at 20° C. The mixture was stirred for 20 min more. Ice-water was added and solution was extracted with dichloromethane. The solvent was evaporated in vacuo yielding 14.0 g (79%) of the desired product.

EXAMPLE 41

5-(3,4-Dihydroxy-6-nitrophenyl)pentanoic acid

A solution containing 42.0 g of the product obtained in Example 40 in 100 ml of acetic acid and 150 ml of 48% hydrobromic acid was reflexed for 10 h. 1 l of saturated Na_2SO_4-solution was added to the reaction mixture and extracted with ether. The solvent was evaporated in vacuo and the residue crystallized from ethyl acetate-petroleum ether. Yield 7.9 g (19%), m.p. 111°–114° C.

EXAMPLE 42

3-(3,4-Dimesyloxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 2.0 g of product described in Example 2 and 5 ml of mesyl chloride in 20 ml of N-methylpyrrolidone was heated for 1.5 h at 100° C. After cooling, water was added and the solution was extracted with ether. The solvent was evaporated in vacuo and the residue was crystallized from 1-propanol. Yield 0.14 g, m.p. 181°–184° C.

EXAMPLE 43

N-(1-Adamantyl)-3,4-diacetoxy-5-nitrobenzamide

A solution containing 0.85 g of 3,4-diacetoxy-5-nitrobenzoic acid and 0.32 ml of thionyl chloride and a catalytic amount of N,N-dimethylformamide in 10 ml of toluene was heated for 1 h at 80° C. The solvent was evaporated in vacuo and the residue was dissolved in 5 ml of dichloromethane and added to a mixture containing 0.56 g of 1-aminoadamantane hydrochloride and 0.94 ml of triethylamine in 10 ml of dichloromethane and stirred for 15 min at 0° C. and then 15 min at 20° C. Water was added to the reaction mixture and dichloromethane phase was separated. The solvent was evaporated in vacuo yielding yellow viscous oil 1.2 g (100%).

EXAMPLE 44

N-(1-Adamantyl)-3,4-dihydroxy-5-nitrobenzamide

A solution containing 1.2 g of the product obtained in Example 43 and a catalytic amount of sulfuric acid in 10 ml of methanol was refluxed for 3 h. 20 ml of water was added and on cooling 0.85 g (89.5%) of the desired product was crystallized, m.p. 207°614 208° C.

EXAMPLE 45

4-Cyclohexylcarbonyl-1-(3,4-diacetoxy-5-nitrobenzoyl)piperidine

The procedure described in Example 43 was repeated using 0.58 g of cyclohexylcarbonylpiperidine and 0.38 ml 2,6-lutidine instead of 1-aminoadamantane hydrochloride and triethylamine respectively. Yield 1.2 g (87%), a viscous yellow oil.

EXAMPLE 46

4-Cyclohexylcarbonyl-1-(3,4-dihydroxy-5-nitrobenzoyl)piperidine

The procedure described in Example 44 was repeated using 1.2 g of the product obtained in Example 45. Yield 0.5 g (50%), m.p. 155°–165° C.

EXAMPLE 47

N-Benzyl-3,4-diacetoxy-5-nitrobenzamide

0.75 g of 3,4-diacetoxy-5-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was dissolved in 5 ml of dichloromethane and added to a solution containig 0.27 ml of benzylamine and 0.5 ml of 2,6-lutidine in 7 ml of dichloromethane. Yield 0.95 g (96%), a viscous oil.

EXAMPLE 48

N-Benzyl-3,4-dihydroxy-5-nitrobenzamide

The procedure described in Example 44 was repeated using 0.95 g of the product obtained in Example 47. Yield 0.5 g (68%), m.p. 185°–189° C.

EXAMPLE 49

N-(1-Adamantyl)-3,4-cyclohexylidenedioxy-6-nitrobenzamide

2 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 1.1 g of 1-aminoadamantane and 1.1 ml of triethylamine in 15 ml of dichloromethane. Yield 2.9 g (98%), a viscous oil.

EXAMPLE 50

N-(1-Adamantyl)-3,.4-dihydroxy-6-nitrobenzamide

A solution containing 0.5 g of the product obtained in Example 49 and 0.09 ml of methanesulfonic acid in 8 ml of 98% formic acid was heated for 15 min at 60° C. The solvent was evaporated in vacuo and water was added to the residue. Yield 0.35 g (88%), m.p. 250°–255° C.

EXAMPLE 51

N-(4-Morpholinoethyl)-3,4-cyclohexylidenedioxy-6nitrobenzamide

2.0 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted into the corresponding acid chloride like described in Example 43. It was added to a solution containing 0.9 ml of 4-(2-aminoethyl)morpholine and 1.1 ml of triethylamine in 15 ml of dichloromethane. Yield 2.5 g (89%), a viscous oil.

EXAMPLE 52

N-(4-Morpholine ethyl)-3,4-dihydroxy-6-nitrobenzamide hydromesylate

The procedure described in Example 50 was repeated using 1.95 g of the product obtained in Example 51. Yield 0.8 g (40%), viscous oil. The ^{1}H-NMR-spectrum was in accordance with the alleged structure.

EXAMPLE 53

N-(1-Adamantyl)-3,4-diacetoxy-5-chlorobenzamide

0.7 g of 3,4-diacetoxy-5-chlorobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 1.0 g (95%), a viscous oil.

EXAMPLE 54

N-(1-Adamantyl)-3,4-dihydroxy-5-chlorobenzamide

The product of Example 53 was deacetylated like described in Example 44. Yield 0.6 g (78%), m.p. 244°–247° C.

EXAMPLE 55

N-(1-Adamantyl)-3,4-cyclohexylidenedioxy-6-chlorobenzamide

0.8 g of 3,4-cyclohexylidenedioxy-6-chlorobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 1.0 g (83%), viscous oil.

EXAMPLE 56

N-(1-Adamantyl)-3,4-dihydroxy-6-chlorobenzamide

1.0 g of the product obtained in Example 55 was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.65 g (81%), m.p. 225°–230° C.

EXAMPLE 57

N-(1-Adamantyl)-3,4-diacetoxy-5-cyanobenzamide

0.6 g of 3,4-diacetoxy-5-cyanobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 0.75 g (88%), viscous oil.

EXAMPLE 58

N-(1-Adamantyl)-3,4-dihydroxy-5-cyanobenzamide

0.75 g of the above product was deacetylated as described in Example 44. Yield 0.5 g (89%), m.p. 253°–255° C.

EXAMPLE 59

1-Butyl-3,4-dihydroxy-5-cyanobenzoate

A solution containing 0.5 g of 3,4-dihydroxy-5-cyanobenzoic acid in 10 ml of 1-butanol was saturated with gaseous hydrogen chloride at 0° C. The solution was then heated for 3 h at 100° C. The solvent was evaporated in vacuo and dichloromethane was added to the residue. The formed crystals were filtered. Yield 0.19 g (30%), m.p. 135°–140° C.

EXAMPLE 60

ω-(2-Methylpiperidyl)-3,4-dimethoxy-6-cyanopropionanilide

A mixture containing 2.68 g of ω-chloro-3,4-dimethoxy-6cyanopropionanilide, 1.5 g of 2-methylpiperidine, 1.4 g of CaO and a catalytic amount of potassium iodide in 15 ml of toluene was heated for 18 h at 100° C. The solution was filtered, washed with water and evaporated in vacuo. The residue was treated with petro-

leum ether and filtered. Yield 2.79 g (84%), m.p. 126°–127° C.

EXAMPLE 61

ω-(1-Adamantylamino)-3,4-dimethoxy-6-cyanopropionanilide

A mixture containing 3.0 g of ω-chloro-3,4-dimethoxy-6cyanopropionanilide, 2.3 g of 1-aminoadamantane hydrochloride, 4.6 g of potassium carbonate and a catalytic amount of potassium iodide in 15 ml of toluene was heated while stirring for 6 h at 100° C. The solution was filtered and the solvent evaporated in vacuo. water was added to the residue and the product was filtered. Yield 3.4 g (74%), m.p. 137°–140° C.

EXAMPLE 62

1-(3,4-Cyclohexylidenedioxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.5 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 0.35 g of 4-cyclohexylcarbonylpiperidine and 0.2 g of triethylamine in 30 ml of dichloromethane. Yield 0.7 g (85%), m.p. 270° C.

EXAMPLE 63

1-(3,4-Dihydroxy-6-nitrobenzyl)-4-cyclohexylcarbonylpiperidine

0.48 g of the above product was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.3 g (75%), m.p. 240° C.

EXAMPLE 64

1-(3,4-Cyclohexylidenedioxy-6-nitrobenzoyl)-4-(1-piperidyl)piperidine

The procedure described in Example 62 was repeated using 0.3 g of 4-(1-piperidyl)piperidine instead of 4-cyclohexylcarbonylpiperidine. Yield 0.57 g (74%), m.p. 200° C.

EXAMPLE 65

Cyclohexyl-4-[1-(3,4-cyclohexylidenedioxy-6-nitrobenzoyl)piperidyl]carbinol

To a solution containing 0.5 g of the product obtained in Example 62 and 1.1 ml of 1N NaOH in 20 ml of methanol 0.1 g of sodium borohydride was added at room temperature. The solution was acidified with acetic acid and extracted with dichloromethane. The solvent was removed in reduced pressure and the residue treated with petroleum ether. Yield 0.45 g (90%), m.p. 155° C.

EXAMPLE 66

1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-(1-piperidyl)piperidine hydromesylate

0.3 g of the product obtained in Example 64 was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.26 g (84%), m.p. 290° C.

EXAMPLE 67

1-(3,4-Diacetoxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.5 g of the product obtained in Example 63 was heated in 10 ml of acetic anhydride for 1 h at 40° C. Ice-water was added and the product was filtered. Yield 0.5 g (87%), m.p. 160°–165° C.

EXAMPLE 68

N-Methyl-N-propargyl-3,4-cyclohexylidenedioxy-6nitrobenzamide

0.5 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride and added to a solution containing 0.12 g methylpropargylamine and 0.18 g of triethylamine in 20 ml of dichloromethane. Yield 0.3 g (50%), m.p. 50°–55° C.

EXAMPLE 69

1-(3,4-Dimethoxy-6-nitrobenzoyl)-4-cyclohexylcarbonyl piperidine

10.3 g of 3,4-dimethoxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 8.83 g of 4-cyclohexylcarbonylpiperidine and 4.58 g of triethylamine in 300 ml of dichloromethane. Yield 16.4 g (90%), m.p. 120°–125° C.

EXAMPLE 70

1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-cyclohexylcarbonyl-piperidine

A solution containing 0.81 g of the above compound in 12 ml of 1 molar BBr_3—CH_2Cl_2 was stirred over night at 20° C. Water was added and the product was filtered. Yield 0.5 g (67%), m.p. 240° C.

EXAMPLE 71

Cyclohexyl-4-[1-(3,4-dimethoxy-6-nitrobenzoyl)-piperidyl]carbinol

2.03 g of the product obtained in Example 69 was reduced with sodium borohydride as described in Excample 65. Yield 1.89 g (93%), m.p. 145°–150° C.

EXAMPLE 72

3-(3-Ethoxycarbonylmethylcarbamoyloxy-4-hydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

1.5 g of ethyl isocyanatoacetate was added to a solution containing 0.54 g of the product obtained in Example 8 in 10 ml of tetrahydrofuran and the solution was stirred for 3 days at 20° C. The solvent was evaporated in reduced pressure and the raw product was purified in a silica gel column using toluene-dioxane-acetic acid (8:1:1) as an eluent. Crystallization from acetone-petroleum ether yielded 0.13 g (17%) of the desired product desired, m.p 155°–158° C.

EXAMPLE 73

3-(3,4-Methylenedioxy-6-nitrophenyl)-1-phenylprop-2-en-1-one

The procedure described in Example 8 was repeated by using 1.95 g of 6-nitropiperonal and 2.10 g of 3',4',5'-trimethoxyacetophenone in 30 ml of methanol. Yield 0.88 (24%), m.p. 157°–159° C.

EXAMPLE 74

3-(4-Hydroxy-3-methoxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated by using 2.0 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde and 2.1 g of 3',4',5'-trimethoxyacetophenone. Yield 2.2 g (57%), m.p. 123°–125° C.

EXAMPLE 75

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(2-carboxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.64 g of 2'-carboxyacetophenone. Yield 0.36 g (11%), m.p. 178-180° C.

EXAMPLE 76

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-nitrophenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.65 g of 4'-nitroacetophenone. Yield 1.25 g (38%), m.p. 255°-256° C.

EXAMPLE 77

3-(3-methoxy-4-hydroxy-5-trifluoromethylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated using 2.2 g of 3-methoxy-4-hydroxy-5-trifluoromethylbenzaldehyde and 2.1 g of 3',4',5'-trimethoxyacetophenone Yield 2 6 g (61%), m,p, 190°-192° C.

EXAMPLE 78

4-(3,4-Dimethoxy-5-methylsulfonylphenyl)-3-methyl-but-3-en-2-one

The procedure described in Example 8 was repeated using 2.44 g of 3,4-dimethoxy-5-methylsulfonylbenzaldehyde and 1.0 g of 2-butanone. Yield 2.0 g (63%), viscous oil.

EXAMPLE 79

2,5-Bis-(3,4-dihydroxy-5-nitrobenzylidene)cyclopentanone

The procedure described in Example 8 was repeated using 5.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.0 g of cyclopentanone. Yield 4.4 g (78%), m.p. 300° C. (decomp.).

EXAMPLE 80

1-Phenyl-3-(3-stearoyloxy-4-hydroxy-5-nitrophenyl)-prop-2-en-1-one

A solution containing 2.0 g of the product obtained in Example 8 and 10.0 g of stearoyl chloride in 10 ml of dioxane was stirred and heated for 18 h at 90° C. After cooling petroleum ether was added and the product was filtered. Recrystallization from dichloromethane-petroleum ether yielded 0.64 g (17%) of the desired product desired, m.p. 112°-118° C.

EXAMPLE 81

Ethyl 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate

The procedure described in Example 4 was repeated using 1.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 0.9 g of ethyl cyanoacetate and 0.15 g of ammonium acetate in 10 ml of ethanol. Yield 0.87 g (57%), m.p. 205°-210° C.

EXAMPLE 82

Methyl 3-(3,4-dihydroxy-5-nitrobenzylidine)-4-ketopentanoate

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.1 g of levulinic acid in 10 ml of methanol was saturated with gaseous hydrogen chloride. The mixture was refluxed for 20 h after which water was added and the solution was extracted with ether. The solvent was evaporated in reduced pressure and the residue crystallized from ether-petroleum ether. Yield 0.54 g (20%), m.p. 142°-150° C.

EXAMPLE 83

3,4-Dihydroxy-5-nitrobenzylmalonitrile

1.5 g of sodium borohydride was added to a suspension containing 3.7 g of the product obtained in Example 5 in 10 ml of water at room temperature. The solution was stirred for 2 h more, acidified with hydrochloric acid and extracted with ether. The solvent was evaporated in vacuo and the residue crystallized from methanol-isopropanol. Yield 1.1 g (30%), m.p. 211°-215° C.

EXAMPLE 84

Ethyl 3,4-dihydroxy-5-nitrobenzylcyanoacetate

The procedure described in Excample 83 was repeated using 2.78 g of the product obtained in Example 81. Yield 0.98 g (35%), yellow viscous oil.

EXAMPLE 85

1-Phenyl-3-(3-methoxy-4-hydroxy-5-trifluoromethylphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.7 g of 3-methoxy-4-hydroxy-5-trifluoromethylbenzaldehyde and 1.0 g of acetophenone. Yield 1.1 g (45%), m.p. 166°-168° C.

EXAMPLE 86

1-Phenyl-3-(3,4-dihydroxy-5-trifluoromethylphenyl)-prop-2-en-1-one

To a solution containing 0.32 g of the above product obtained in Example 85 in 10 ml of dichloromethane 3 ml of 1 molar BBr3-CH2C12 was added. The mixture was stirred for 20 min at room temperature, acidified with 10 ml 2 N hydrochloric acid and extracted with dichloromethane. The solvent was evaporated in reduced pressure and the residue crystallized from acetone-dichloromethane. Yield 0.07 g (23%), m.p. 196°-201° C.

EXAMPLE 87

3,4-Dihydroxy-5-sulfonamidobenzaldehyde

A solution containing 1.89 g of 2,3-dihydroxybenzenesulfonamide and 1.4 g of hexamethylenetetramine in 20 ml of trifluoroacetic acid was refluxed for 2 h. The solvent was evaporated in vacuo, water was added to the residue and the product was filtered. Yield 0.78 g (35%).

EXAMPLE 88

2-Methoxy-6-trifluoromethylphenol

A solution containing 160 ml of 1.6 molar butyllithium in hexane, 300 ml of tetrahydrofuran and 40 ml of N,N,N',N'-tetramethylethylenediamine was cooled to −78° C. and 43.3 g of 3-trifluoromethylanisole was added with stirring under nitrogen atmosphere. The solution was allowed to warm up to room temperature and cooled then again to −78° C. after which 35 ml of trimethyl borate was added. The solution was warmed up to 20° C. and 50 ml of conc. ammonia solution was

added. The solvents were evaporated in reduced pressure and to the residue 60 ml of 98–100% formic acid followed with 25 ml of 35% hydrogen peroxide were added. The solution was extracted with ether-petroleum ether (1:1). The organic phase was separated and the product was extracted with 2.5 N NaOH-solution. The aqueous phase was acidified with hydrochloric acid and the product was extracted in dichloromethane. The solvent was removed for the most part in vacuo after which petroleum ether was added. The crystalline product was filtered, yield 8.5 g (18%), m.p. 51°–53° C.

EXAMPLE 89

4-Hydroxy-3-methoxy-5-trifluoromethylbenzaldehyde

A solution containing 1.9 g of 2-methoxy-6-trifluoromethylphenol and 1.4 g of hexamethylenetetramine in 20 ml of trifluoroacetic acid was refluxed for 1 h. The solvent was removed in reduced pressure, 50 ml of 1 N hydrochloric acid was added to the residue and the solution was extracted with dichloromethane. Most part of the solvent was evaporated in vacuo and petroleum ether was added, whereupon the product crystallized. Yield 0.7 g (32%), m.p. 151°–152° C.

EXAMPLE 90

3,4-Dimethoxy-5-cyanobenzaldehyde

A mixture containing 2.5 g of 3,4-dimethoxy-5-bromobenzaldehyde and 1.0 g of cuprous cyanide in N-methylpyrrolidone was refluxed for 2 h. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated in vacuo. Yield 1.55 g (81%), m.p. 109°–112° C.

EXAMPLE 91

3,4-Dihydroxy-5-cyanobenzaldehyde

A solution containing 0.96 g of the above product in 15 ml of 1 molar BBr_3—CH_2Cl_2-solution was stirred for 4 h at room temperature under nitrogen. 15 ml of 1 N hydrochloric acid was added and the dichloromethane phase was separated. The solvent was evaporated in vacuo. Yield 0.61 g (75%), m.p. 210°–215° C.

EXAMPLE 92

1,2-Dimethoxy-3-methylsulfonylbenzene

To a solution containing 3.68 g of 2,3-dimethoxythioanisole in 50 ml of dichloromethane 3.6 g of 3-chloroperoxybenzoic acid was added with stirring. Stirring was continued for 18 h more at room temperature. 30 ml of 1 N NaOH-solution was added, dichloromethane phase was separated and the solvent evaporated in vacuo. Yield 4.51 g (91%), a viscous oil.

EXAMPLE 93

3,4-Dimethoxy-5-methylsulfonylbenzaldehyde

The procedure described in Example 89 was repeated using 2.16 g of 2 hexamethylenetetramine. Yield 0.97 g (45%), a viscous oil.

EXAMPLE 94

3,4-Dihydroxy-5-methylsulfonylbenzaldehyde

A solution containing 0.5 g of the above product and 5 ml of 48% hydrobromic acid in 5 ml of acetic acid was refluxed for 8 h. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated in vacuo. Yield 0.3 g (68%), a viscous oil.

EXAMPLE 95

3,4-Dihydroxy-5-cyanobenzaldehyde

A solution containing 1.35 g of 2,3-dihydroxybenzonitrile and 1.4 g of hexamethylene tetramine in 20 ml of trifluoroacetic acid was refluxed for 1.5 h. Water was added and the product was filtered. Yield 0.9 g (55%), m.p. 211°–215° C.

EXAMPLE 96

3-(3,4-Dihydroxy-5-trifluoromethylphenyl)-1-phenyl-prop-2-en-1-one

The procedure described in Example 8 was repeated using 2.06 g of 3,4-dihydroxy-5-trifluoromethylbenzaldehyde and 1.20 g of acetophenone. Yield 2.19 g (71%), m.p. 196°–210° C.

EXAMPLE 97

3,4-Dihydroxy-5-trifluoromethylbenzaldehyde

A solution containing 2.2 g of 4-hydroxy-3-methoxy-5-trifluoromethylbenzaldehyde in 65 ml of 1 molar BBr_3 in dichloromethane was stirred for 2 h at room temperature. Hydrochloric acid was added and the organic phase was separated. The solvent was evaporated in vacuo. Yield 1.4 g (68%), m.p. 188°–192° C.

EXAMPLE 98

2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

A solution containing 1.3 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 0.73 g of cyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. The solvent was evaporated in vacuo and the residue was recrystallized water-DMF. Yield 0.84 g (48%), m.p. 296°–298° C.

EXAMPLE 99

N,N-Dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 1.2 g of N,N-dimethylcyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. Yield 1.1 g (40%), m.p. 183°–185° C.

EXAMPLE 100

N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl-)acrylamide

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.5 g of N,N-diethylcyanoacetamide. Yield 2.23 g (73%), m.p. 153°–156° C.

EXAMPLE 101

N-Isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl-)acrylamide

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.3 g of N-isopropylcyanoacetamide. Yield 1.46 g (50%), m.p. 243°–245° C.

EXAMPLE 102

N'-Methyl-N''-[2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acryl]piperazine

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.7 g of N'-methyl-N''-cyanoacetylpiperazine. Yield 2.16 g (65%), m.p. 65° C. (decomp.).

EXAMPLE 103

3-(3,4-Dihydroxy-5-trifluoromethylbenzylidene)-2,4-pentanedione

The procedure described in Example 7 was repeated using 2.06 g of 3,4-dihydroxy-5-trifluoromethyl-benzaldehyde and 1.00 g of 2,4-pentanedione. Yield 1.39 g (45%), m.p. 98°–205° C.

EXAMPLE 104

3,4-Dihydroxy-5-nitrobenzylalcohol

To a solution containing 6.0 g of sodium borohydride in 50 ml of water 9.15 g of 3,4-dihydroxy-5-nitrobenzaldehyde was gradually added with stirring at room temperature. The mixture was stirred for 1 h more after which it was acidified with hydrochloric acid. The solution was filtered to remove tarry impurities and extracted 4 times with ether. The ether extract was dried over anhydrous sodium sulfate, filtered and concentrated to a volume of about 100 ml.

The crystalline solid was filtered. Yield 6.0 g (65%), m.p. 100° C. (decomp.).

EXAMPLE 105

3,4-Dihydroxy-5-nitrobenzyl-2-methoxyethyl ether

A solution of 1.0 g of 3,4-dihydroxy-5-nitrobenzylalcohol in 5.0 ml of 2-methoxyethanol was refluxed for 1 h. The solvent was evaporated in vacuo and the residue was triturated with isopropanol. Yield 0.4 g (30%), m.p. 154°–157° C.

EXAMPLE 106

3,4-Dihydroxy-5-nitrobenzylthioacetic acid

A solution containing 1.0 g of 3,4-dihydroxy-5-nitrobenzylalcohol in 5.0 g of thioglycolic acid was stirred for 1.5 h at 120° C. 25 ml of water was added and product was filtered and washed with water. Yield 0.25 g (19%), m.p. 91°–93° C.

EXAMPLE 107

2-(3,4-Dihydroxy-5-nitrobenzyl)pyrrole

A solution containing 1.0 g of 3,4-dihydroxy-5-nitrobenzyl alcohol and 5.0 ml of pyrrole in 3.0 ml of dioxane was heated for 5 h at 100° C. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated and the residue was purified in a silicagel column using toluene-acetic acid-dioxane (18:1:1) mixture as an eluent. Yield 0.42 g (33%), m.p. 115°–118° C.

EXAMPLE 108

2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)propanol

To a solution containing 0.85 g of ethyl 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate (Example 81) in 70 ml of dry ethanol 0.3 g of sodium borohydride was gradually added. The solution was stirred for 0.5 h at room temperature, acidified with hydrochloric acid and extracted with ethyl acetate. The solvent was evaporated yielding 0.55 g (75%) of yellow crystals, m.p. 149°–152° C.

EXAMPLE 109

3-Nitrocatechol

To a solution containing 2.5 g of catechol in 125 ml of ether 1.0 ml of conc. nitric acid (d-1.52) was gradually added. The solution was stirred over night at room temperature and washed with water. The solvent was evaporated and the residue was treated with boiling petroleum ether (b.p. 60°–80° C). The insoluble 4-nitrocatechol was filtered and the filtrate concentrated in vacuo. After cooling the 3-nitrocatechol was filtered. Yield 0.85 g (24%), m.p. 82°–85° C.

EXAMPLE 110

3,5-Dinitrocatechol

To a solution containing 50.0 g of catechol diacetate in 250 ml of acetic acid 125 ml of nitric acid (d-1.42) was gradually added at 50° C. The solution was stirred for 1.5 h more at 50° C. and poured then to crushed ice. The product was filtered, washed with water and dissolved in 500 ml of methanol containing 1.0 ml of conc. sulfuric acid. The solution was refluxed for 2.5 h. Methanol was distilled off to a great ,extend and 100 ml of water was added. The remaining methanol was evaporated in vacuo whereupon the product was crystallized. Yield 20.9 g (40.4%), m.p. 168°–170° C.

EXAMPLE 111

3,4-Dihydroxy-5-nitrobenzaldehyde

A solution containing 8.0 kg of 5-nitrovanillin and 8.7 kg of acetic acid in 35 kg of conc. hydrobromic acid was refluxed for 20 h. 0.6 kg of charcoal was added and the mixture was filtered. 32 kg of water was added with stirring and the solution was cooled to −10° C. and stirring was continued for 2 h more. The crystalline product was filtered and washed with water. Yield 5.66 kg (80%), m.p. 135°–137° C.

EXAMPLE 112

3,4-Dihydroxy-5-nitrobenzonitrile

A solution containing 0.92 g of 3,4-dihydroxy-5-nitrobenzaldehyde. and 0.49 g of hydroxylamine hydrochloride in 5.0 ml of formic acid was refluxed for 1 h. 50 ml of water was added and the product was filtered and washed with water. Yield 0.3 g (33%), m.p. 175°–178° C.

EXAMPLE 113

4-Chloro-6-nitrocatechol

A mixture containing 1.0 g of 4-chloro-3-methoxy-6nitrophenol in 20 ml of conc. hydrobromic acid was refluxed for 2 h. After cooling the product was filtered and washed with water. Yield 0.6 g (65%), m.p. 108°–111° C.

EXAMPLE 114

4,5-Dihydroxyisophthalaldehyde

To a suspension containing 1.8 g of 4-hydroxy-5-methoxyisophthalaldehyde in 20 ml of dichloromethane was added 35 ml of 1 molar PBr_3 in dichloromethane. The mixture was allowed to stand over night at room temperature and poured into ice-water, Dichloromethane was evaporated in vacuo. After cooling the product

was filtered and washed with wash. Yield 0.94 g (57%), m.p. 192°–195° C.

EXAMPLE 115

3,4-Dihydroxy-5-cyanobenzoic acid

To a solution containing 2.3 g of 4-acetoxy-3-cyano-5-methoxybenzoic acid in 10 ml of dichloromethane 40 ml of 1 molar PBr_3 in dichloromethane was added. The mixture was stirred ever night at room temperature. The solvent was evaporated in vacuo and to the residue ice-water was added. The product was filtered and washed with water. Yield 1.25 g (74%), m.p. 269°–271° C.

EXAMPLE 116

3,4-Dihydroxy-5-nitrophenylalamine hydrobromide

A solution containing 1.2 g of 4-hydroxy-3-methoxy-5-nitrophenylalanine hydrosulfate in 10 ml of conc. hydrobromic acid was refluxed for 2 h. The solution was concentrated in vacuo and allowed to stand over night in a refrigerator. The product was filtered and washed with hydrobromic acid and dried. Yield 0.25 g, m.p. 170° C. (decomp.).

EXAMPLE 117

3,5-Dicyanocatechol

A solution containing 0.83 g of 3,5-diformylcatechol and 0.90 g of hydroxylamine hydrochloride in 30 ml of formic acid was refluxed for 16 hours. Formic acid was evaporated in vacuo and water was added to the residue. The solution was extracted with ether. The solvent was evaporated and the residue was crystallized from ethanol-water. Yield 0.28 g (43%), m.p. 300° C, (decomp.).

EXAMPLE 118

N,N-diethyl-5-chloro-2,3-dihydroxybenzenesulfonamide

To a solution containing 0.7 g of N,N-diethyl-5-chloro-3,4-dimethoxybenzenesulfonamide in 10 ml of dichloromethane 9.0 ml of 1 molar BBr_3 in dichloromethane was added. The solution was stirred overnight at room temperature. Water and hydrochloric acid were added and the mixture was extracted with dichloromethane. The solvent was evaporated. Yield 0.3 g (47%), m.p. 62°–64° C.

EXAMPLE 119

4-Chloro-6-methylsulfonylcatechol

The procedure described in Example 118 was repeated using 4-chloro-2-methoxy-6-methylsulfonylphenol. Yield 50%, m.p. 142°–145° C.

EXAMPLE 120

4-Nitro-6-methylsulfonylcatechol

The procedure described in Example 118 was repeated using 2-methoxy-4-nitro-6-methylsulfonylphenol. Yield 21%, m.p. 221°–224° C.

EXAMPLE 121

3,4-Dihydroxy-5-methylsulfonylbenzaldehyde

The procedure described in Example 118 was repeated using 4-hydroxy-3-methoxy-5-methylsulfonylbenzaldehyde. Yield 17%, m.p. 169°–171° C.

EXAMPLE 122

N-(3-hydroxypropyl)-3,4-dihydroxy-5-nitrobenzamide

The procedures described in Examples 43 and 44 were repeated using 3,4-diacetoxy-5-nitrobenzoic acid and 3-aminopropan-1-ol. Yield 85%, m.p. 160°–163° C.

EXAMPLE 123

Neopentyl
2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate

The procedure described in Example 4 was repeated using 3,4-dihydroxy-5-nitrobenzaldehyde and neopentyl cyanoacetate. Yield 67%, m.p. 173°–179° C.

EXAMPLE 124

N-(3-hydroxypropyl)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

The procedure described in Example 99 was repeated using N-(3-hydroxypropyl)cyanoacetamide and 3,4-dihydroxy-5-nitrobenzaldehyde. Yield 52%, m.p. 223°–228° C.

EXAMPLE 125

2,3-Dihydroxy-5-nitrobenzonitrile

The procedure described in Example 118 was repeated using 2-hydroxy-3-methoxy-5-nitrobenzonitrile. Yield 45%.

EXAMPLE 126

3,5-Dicyanocatechol

To a solution containing 2,4-dicyano-6-methoxyphenol in 20 ml of dichloromethane 20 ml of 1 molar solution of BBr_3 in dichloromethane was added. The solution was stirred overnight at room temperature. Water and hydrochloric acid were added and the mixture was extracted with dichloromethane. The solvent was evaporated. Yield 0.8 g (50%), m.p. 300° C. (decomp.).

EXAMPLE 127

1,2-Diacetoxy-3,5-dinitrobenzene

A catalytic amount of concentrated sulfuric acid was added to a solution containing 2.0 g of 3,5-dinitrocatechol in 15 ml of acetanhydride and the solution was mixed for ½ hours in 50°–60° C. Ice water was added to the rection mixture and the solution was mixed in 0° C. whereby the product was crystallized. The product was filtered and washed with water and dried. Yield 2.75 g (97%), m.p. 115°–117° C.

EXAMPLE 128

1,2-Dipropionyloxy-3,5-dinitrobenzene

The procedure of Example 127 was repeated using propionic acid anhydride instead of acetanhydride. Yield 2,8 g (90%), m.p. 72°–73° C.

EXAMPLE 129

1,2-Dibutyryloxy-3,5-dinitrobenzene

The procedure described in Example 127 was repeated using butyrylanhydride instead of acetanhydride. Yield 70%, m.p. 65°–60° C.

EXAMPLE 130

2-Butanoyloxy-4,6-dinitrophenol

8.7 ml of nitric acid (d-1.42) was added stirring and cooling to a solution containing 2.4 g of catechol dibutyrate in 25 ml of acetic acid. The solution was stirred for further ½ hours and ice water was added thereto. The product was filtered and washed with water. Yield 1.85 g (53%), m.p. 65°–70° C.

EXAMPLE 131

2-Pivaloyloxy-4,6-dinitrophenol

6.7 ml of nitric acid (d-1.42) was added stirring and cooling (in 20°–25° C.) to a solution containing 1.94 g of catechol monopivaloate in 20 ml of acetic acid. The solution was stirred for ½ hours in 50° C. Ice water was added and the product was filtered and washed with water. Yield 1.75 g (62.5%). m.p. 132°–135° C.

EXAMPLE 132

2-Benzoyloxy-4,6-dinitrophenol

A mixture containing 2.0 g of 3,5-dinitrocatechol in 5 ml of benzoylchloride was cooked for 4 hours in 100° C. When cooled petroleum ether (b.p. 40° C.) was added and the product was filtered and washed with petroleum ether. The raw product was crystallized from ethanol. Yield 2.5 g (82%), m.p. 150°–152° C.

EXAMPLE 133

3-(4-Hydroxy-5-nitro-3-pivaloyloxybenzylidene)-2,4-pentanedione

A mixture containing 2.0 g of the product obtained according to Example 7 in 5 ml of pivaloylchloride was heated for 4 hours in 100° C. The excess pivaloylchloride was evaporated away in reduced pressure and ether was added to the residue. The product was filtered and washed with ether. Yield 1.41 g (58%), m.p. 143°–145° C.

EXAMPLE 134

2-(2,6-Dimethylbenzoyloxy)-4,6-dinitrophenol

A mixture containing 2.0 g of 3,5-dinitrocatechol in 5 ml of 2,6-dimethylbenzoylchloride was heated for 20 hours in 100° C. The excess 2,6-dimethylbenzoylchloride was removed in high vacuum. The residue was purified in silicagel column. Yield 1.5 g (45%), yellow viscous oil, which was crystallized from petroleum ether, m.p. 163°–165° C.

EXAMPLE 135

2-(2,6-Dimethoxybenzoyloxy)-4,6-dinitrophenol

The procedure of Example 134 was repeated using 2,6-dimethoxybenzoylchloride. Yield 1.3 g (36%), m.p. 217°–218° C.

EXAMPLE 136

2-(1-Methylcyclohexylcarbonyloxy)-4,6-dinitrophenol

The procedure of Example 134 was repeated using 1-methylcyclohanecarboxylic acid chloride. Yield 1.6 g (49%), yellow

EXAMPLE 137

1,2-Bis(2,6-dimethylbenzoyloxy)-3,5-dinitrobenzene

The procedure of Example 134 was repeated using a temperature of 134° C. The product was crystallized from 50% ethanol. M.p. 175°–178° C. Yield 60%.

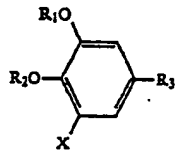
EXAMPLE 138

1,2-Bis(3-ethoxycarbonylpropionyloxy)-3,5-dinitrobenzene

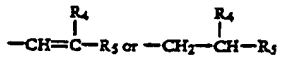
A solution containing 1 g of 3,5-dinitrocathecol in 2,5 ml of ethyl ester chloride of succinic acid was heated for 3 h in 100° C. The product was purified in silicagel column. M.p. 60°–63° C.

What is claimed is:

1. A compound according to formula I



wherein R_1 and R_2 independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents nitro or cyano and R_3 represents



wherein R_4 represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R_5 represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof.

2. The compound according to claim 1, wherein R_4 is cyano and R_5 is carbamoyl which is unsubstituted or substituted with alkyl of 1 to 3 carbon atoms.

3. N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

4. A compound selected from the group consisting of 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl-)acrylamide and N-isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide.

* * * * *

EXHIBIT 4

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,446,194	183	940	----	08/121,617	08/29/95	09/16/93	04	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	020325053

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

EXHIBIT 5

COMBINED DECLARATION AND POWER OF ATTORNEY FOR UTILITY PATENT APPLICATION	Attorney Docket No. 020325-030

As a below-named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (if only one name is listed below) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (if more than one name is listed below) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION

ENTITLED: PHARMACOLOGICALLY ACTIVE COMPOUNDS, METHODS FOR THE PREPARATION THEREOF AND COMPOSITIONS CONTAINING THE SAME

the specification of which

(check one) ☐ is attached hereto;
☒ was filed on November 27, 1987 as
Application Serial No. 07/126,911
and was amended on 11/27/87, 6/13/89, 11/28/89, 3/30/90 ; (if applicable)

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE;

I ACKNOWLEDGE THE DUTY TO DISCLOSE INFORMATION WHICH IS MATERIAL TO THE EXAMINATION OF THIS APPLICATION IN ACCORDANCE WITH TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (a) which states: "A duty of candor and good faith toward the Patent and Trademark Office rests on the inventor, on each attorney or agent who prepares or prosecutes the application and on every other individual who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application. All such individuals have a duty to disclose to the Office information they are aware of which is material to the examination of the application. Such information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. The duty is commensurate with the degree of involvement in the preparation or prosecution of the application.";

I do not know and do not believe the said invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than twelve months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code Sec. 119 and/or Sec. 365 of any foreign application(s) for patent or inventor's certificate as indicated below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application(s) on which priority is claimed:

COMBINED DECLARATION AND POWER OF ATTORNEY		Attorney Docket No. 020325-030	
COUNTRY/INTERNATIONAL	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
FI	864875	28 Nov 1986	YES XX NO__
GB	8712437	27 May 1987	YES XX NO__

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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